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FROM THE EDITOR-IN-CHIEF

Ethics of Prescription Medication Access, Innovation, and Prescribing

Audiey C. Kao, MD, PhD

It wasn't that long ago when few prescription medications were available to treat what ailed patients. Today, more than three-quarters of all physician office visits involve some kind of drug therapy ranging from analgesics and antihypertensives to antibiotics and antidepressants.¹ In 2017, prescription medications made up about 10% of all personal health care spending, or almost \$335 billion.² While these medications offer important benefits, they can also be very expensive, as 1 in 4 patients report having difficulty paying for their medications.³ Therefore, it isn't surprising that more than two-thirds of Americans see it as a top priority for Congress to lower prescription medication costs.⁴

This issue of the *AMA Journal of Ethics* explores the topic of prescription medications from many angles. Novel—and very costly—medications designed to cure and not simply treat medical conditions have arrived. Pete Croughan and Rebekah E. Gee examine how physicians can better allocate medication via a [subscription payment model](#)—in this case, for curing hepatitis C infections—when there are limited Medicaid resources to cover the health care needs of low-income patients. Currently, 1 in 5 Americans rely on Medicaid coverage.⁵ Jennifer A. Ohn and Anna Kaltenboeck evaluate state Medicaid programs' reliance on [drug rebates](#) from pharmaceutical companies in exchange for maintaining an open formulary and consider whether closed formularies too narrowly restrict access to some medications. Leah Rand and Govind Persad argue that [Medicaid closed formularies](#) are ethically justifiable as a way of restraining drug spending if they result in public expenditures on other socially valuable uses that promote health, such as early childhood education. To further promote more equitable drug access, Michael J. DiStefano and Jonathan S. Levin advocate using [cost-effectiveness analysis](#) alongside decision-making tools that incorporate equity considerations and promote transparency to inform prescribing policy and decisions.

Pharmaceutical and biotechnology companies are motivated in part by profits they make from medications they bring to the market. Balancing this profit motive with promoting affordable access to medications has been a policy focus for decades. In her review of the Drug Pricing Competition and Patient Term Restoration Act of 1984 (more commonly referred to as the [Hatch-Waxman Act](#)), Jordan M. Warhol argues that the act's goal of balancing drug innovation and availability has been undermined by pay-for-delay arrangements that slow market arrival of competing generic drugs. As part of the Patient Protection and Affordable Care Act of 2010, Congress passed the Biologics Price

Competition and Innovation Act, modeled loosely on the Hatch-Waxman Act. Mike Z. Zhai, Ameet Sarpatwari, and Aaron S. Kesselheim examine why few [biosimilars](#) are currently available and argue that one reason for the lack of competitors could be biologics companies' delay arrangements.

For those who prescribe medications, it is safe to say that many have no idea how generic drug names are assigned. Gail B. Karet describes the United States Adopted Names (USAN) Program, which is overseen by the American Medical Association, the United States Pharmacopeial Convention, and the American Pharmacists Association. She shows that [USAN assignments of generic drug names](#) have wide-ranging implications, from patient safety to drug pricing. From a medical education perspective, Rohanit Singh and Gary W. Pushkin argue that more ethics training is necessary to better prepare physicians to appropriately prescribe opioids.

Finally, 3 works of art are presented in this issue. Alana Noelle Snyder assembled a mixed media collage from magazine drug advertisement fragments to promote reflection about the influence of [pharmaceutical marketing](#) on patient-physician relationships. Tracy Meyer created a series of drawings inspired by seeds, which suggest that the [innovation ecosystem](#) must be nurtured for future medication breakthroughs to occur. Through graphic narrative, Hannah Rebeccah Abrams tells a story of how hospitals struggled through a [shortage of normal saline solution](#) after Hurricane Maria devastated key pharmaceutical suppliers based in Puerto Rico.

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CASE AND COMMENTARY

How Should Physicians Steward Limited Resources While Ensuring That Patients Can Access Needed Medicines?

Pete Croughan and Rebekah E. Gee, MD, MPH

Abstract

Hepatitis C poses public health and fiscal crises for state Medicaid programs trying to respond to this epidemic. Meager funding streams, a lack of negotiating power, and escalating pharmaceutical prices exacerbate the financial strain placed on these programs as they struggle to meet public health priorities. The Louisiana Department of Health has adopted a subscription model for hepatitis C treatment, but costly medications continue to challenge states' capacities to cover patients who need costly drugs.

Case

Dr X serves as chief medical officer for the state Department of Health and sees patients at a local federally qualified health center. Recently, an exciting, expensive new drug was released, which cures all strains of hepatitis C. The state Department of Health approaches Dr X to help draw up Medicaid access guidelines for this new drug, citing that the state cannot afford to cover this drug for all patients with hepatitis C. The Secretary of the Department of Health asks Dr X to define clinical criteria, such as liver fibrosis stage or substance use status, to help prioritize which patients should have access to the drug under Medicaid. Dr X understands the reality of the state's financial restrictions and agrees to offer a prioritized list of clinical criteria.

Later that week, upon examining the health record of a patient, Mr R, Dr X notices that Mr R has a prior hepatitis C diagnosis. A note in the record suggests that Mr R wasn't approved by Medicaid to receive therapy for hepatitis C because of his continued substance abuse. Mr R has gone through multiple substance abuse treatments in the past and has relapsed back into self-abusive behaviors soon after each treatment. Dr X also notices that Mr R is jaundiced, however, and remains concerned that Mr R has advanced liver damage. Dr X sends Mr R for liver function testing, fearing that Mr R will not qualify for a liver transplant if his test results show poor function. If that's the case, a pharmaceutical agent might be Mr R's best hope for treatment.

Dr X wonders how to balance the need for population-level guidelines about access against interests of individual patients like Mr R.

Commentary

This case demonstrates a tension between fiscal and clinical needs regarding costly prescription drugs for hepatitis C. To help think through this case, we consider how this kind of tension has been managed in Louisiana.

In 2013, hepatitis C killed more Americans than 60 other infectious diseases combined,¹ and it represents a public health and fiscal crisis. The opioid epidemic has furthered the spread of the hepatitis C virus.² According to the Louisiana Office of Public Health, an estimated 89 000 Louisianans are infected with it.³ A large proportion of these individuals have medical expenditures paid by the state, either through Medicaid or the Department of Corrections. However, the high costs of drugs that eliminate this virus—even accounting for federal and supplemental rebates—prohibit the state from providing them to larger numbers of patients. In 2017, Louisiana treated less than 3% of known hepatitis C infections among patients covered by Medicaid.⁴

Some Medicaid programs are now seeking to leverage substantial [decreases in pharmaceutical costs](#) through new strategies such as closed formularies and spending growth caps.⁵ Although the [Medicaid Drug Rebate Program](#) confers a notable benefit of guaranteeing Medicaid programs' access to the best price in the market, it also requires state programs to cover almost every medication of manufacturers who sign a national rebate agreement with the Secretary of the US Department of Health and Human Services.⁵ According to the Medicaid and Children's Health Insurance Program Payment and Access Commission, total Medicaid spending on outpatient drugs increased 38.2% from 2013 to 2015, largely attributable to the introduction of branded formulations of sofosbuvir, ledipasvir/sofosbuvir, and ombitasvir/paritaprevir/ritonavir and dasabuvir.⁶ Meanwhile, most states are required by law to balance their budget each year,⁷ creating a zero-sum predicament: If one area of the budget increases unexpectedly, another area must be cut to compensate. Where should cuts be made?

Competing Challenges for Sparse Funds

According to the 2018 America's Health Rankings, Louisiana is the least healthy state in the nation.⁸ The hepatitis C crisis is one of many infectious disease crises in Louisiana. Two of 5 US cities with the highest rates of HIV are New Orleans and Baton Rouge (ranked fourth and fifth, respectively, in 2017).⁹ Nationwide, in 2017 Louisiana ranked third in AIDS case rates and third in case rates of primary and secondary syphilis.⁹ In addition to having high rates of infectious diseases, Louisiana is among the states with the highest rates of maternal mortality,¹⁰ diabetes, and smoking.¹¹ When looking for root causes of these health outcomes, one finds that Louisiana has the highest average percentage of people living in poverty in any state,¹² has weathered the largest cuts to state funding for higher education on a per-pupil basis since 2008,¹³ and has had the highest homicide rate in the United States for 29 years in a row.¹⁴

Despite these unmet needs, meager funding streams could still be cut. In budget negotiations for 2018, the Louisiana Department of Health was threatened with more than \$500 million in state general fund reductions. With no solution only weeks prior to the end of the fiscal year, the Department of Health was forced to notify 37 000 seniors and persons with disabilities in nursing homes that their Medicaid eligibility and, in turn, their housing was at risk of being eliminated.¹⁵ Meanwhile, a major academic and safety net hospital in the heart of Cajun country, Lafayette General Health, notified 800 employees that their employment would be terminated if the state was unable to resolve the budget crisis.¹⁶ Fortunately, an agreement was reached, but such notices demonstrate just how tenuous the Medicaid safety net is.

The Subscription Model

Given perennially jeopardized funding streams, the Louisiana Department of Health sought an alternative mechanism to dramatically expand access to treatment for large numbers of persons with hepatitis C without undermining capacity to respond to other critical needs. One alternative mechanism being pursued is the subscription payment model, according to which the state pays drug manufacturers for unlimited access to medications for a specified time period for patients enrolled in Medicaid or in Louisiana's [correctional system](#).¹⁷ This model has also been described as "Netflix style," reflecting the application of subscription-based pricing in the pharmaceutical sector.¹⁸ Payment to a drug manufacturer would be equal to or less than what the state is currently spending to provide antiviral drugs to these populations. Patients with hepatitis C would receive the unrestricted treatment access they deserve, and the drug manufacturer partnered with the state would receive a stable revenue stream and larger market share. A similar model in Australia showed that providing unrestricted access to antivirals for hepatitis C at a cost of US\$766 million over 5 years produced estimated savings of US\$4.9 billion to the Australian government compared to conventional per-unit pricing.¹⁹ Applying the subscription model at the state level in the United States would allow policymakers to pursue hepatitis C elimination without jeopardizing other public health priorities. For clinicians like Dr X, removing the financial barrier to treatment would allow him to make recommendations based solely on his clinical judgment and what's best for patients like Mr R.

Conclusion

States' adoption of the subscription model affords a possible solution to the hepatitis C epidemic. However, in the absence of regulatory or market pressure to broadly reduce the price of pharmaceuticals, state policymakers will continue to struggle to meet the needs of patients requiring high-cost drugs; each new high-cost breakthrough will pit one disease against another and one meaningful public health program against another.

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MEDICAL EDUCATION

How Should Medical Education Better Prepare Physicians for Opioid Prescribing?

Rohanit Singh and Gary W. Pushkin, MD

Abstract

Opioid overprescribing is a key contributor to the current crisis. Changing how ethics is taught in connection with opioid prescribing is one area for improvement. In US medical schools, current training in ethics and opioid prescribing is variable, incorporating a diverse range of concepts, teaching modes, assessment strategies, and faculty experience. This article recommends integrating clinical case-based teaching and longitudinal application, comprehensive assessment, and additional training in ethical deliberation about opioid prescribing to better prepare physicians to responsibly prescribe and manage opioid-based phases of patients' pain care.

Medical Education and Overprescribing

In its current state, the opioid epidemic is a major public health issue that has garnered widespread attention. The National Institute on Drug Abuse reports that more than 130 people die every day as a result of opioid overdose.¹ Opioid overuse also poses a heavy financial burden on the nation, with the Centers for Disease Control and Prevention estimating that \$78.5 billion is spent annually to respond to opioid misuse, addiction treatment, and related health care.¹

Physician overprescribing has been cited as a contributor to the epidemic. Hirsch posits in his evaluation of the causes of the opioid crisis that though most physicians are "well meaning," they often prescribe "30 or 60 pills when 5 or 20 would have been adequate."² In the United States alone, 240 million opioid prescriptions were dispensed in 2015, nearly one for every adult in the general population.³ Between 1999 and 2015, the morphine milligram equivalents per person prescribed in the United States increased from 180 to 640.³

There is evidence that prescribing behaviors are solidified during medical school. A 2006 study concluded that the "root cause" of prescription errors could be attributed to a "lack of a knowledge base that integrated scientific knowledge with clinical know-how."⁴ And a 2017 study published by the National Bureau of Economic Research found a negative correlation between medical school ranking and physician opioid prescribing, possibly

reflecting differences in training about the appropriateness of opioid prescribing.⁵ Such findings demonstrate that there is room for improvement within medical education, especially pertaining to education about the ethics of prescribing opioids. As Stratton et al note, one potential consequence of opioid prescribing that deserves ethical attention is “adequately addressing a patient’s chronic noncancer pain without possibly setting the stage for addiction to opioid medications.”⁶ In this paper, we review the current state of ethical education and opioid-related courses in medical schools and describe strategies for improving training in the ethics of opioid prescribing. Learning from cases that encompass a broad spectrum of patient experiences and histories can better prepare students to identify potential issues such as misuse, diversion, and overdose while not negating the patient’s needs.

Training in Ethics and Prescribing Practices

Variation in pedagogical approaches, core concepts, and methods of teaching more generally underscore the lack of a standardized ethics curriculum within medical schools. A survey of 87 medical schools regarding their medical ethics curriculum elicited a total of 39 different content areas and 8 different modes of teaching, with each school incorporating an average of 4 teaching methods and 13 content areas.⁷ This diversity demonstrates the failure of the educational system to comprehensively address the ethical dimensions of physicians’ roles. Additionally, although a Delphi survey of 55 medical school deans culminated in an agreement on 19 key concepts that were determined to be important for students to learn in ethics courses, only 6 of these concepts—informed consent, health care delivery, confidentiality, quality of life, death and dying, and euthanasia—were taught in over 50% of medical schools that mandated some form of ethical training.⁷ Such findings indicate that many medical schools fail to include key concepts that medical school deans deem vital to physicians’ professional development.

In response to the opioid epidemic, medical schools in the United States are beginning to integrate courses covering pain-related incidents and substance use disorders (SUDs).⁸ A 2018 study undertaken by the Association of American Medical Colleges assessing the curricula of 102 medical schools found that 87% of these schools covered pain domains, including pain assessment, pain management, and [SUD treatment](#).⁸ The means by which medical schools go about immersing their students in these domains, however, varies. Although lectures, clinical experiences, and case-based learning were found in a majority of medical schools, 19 different teaching methods and 8 different assessment approaches were identified.⁸

In addition to the lack of a standardized ethics and prescribing curriculum, another challenge to teaching prescribing ethics is a lack of faculty adequately trained in teaching prescribing ethics and in assessing students’ learning about ethical concepts related to prescribing. Because much of the knowledge surrounding opioid prescribing and pain

management in particular has emerged only recently, many medical schools find that there is a lack of adequately experienced faculty to teach these topic areas and assess medical students' learning.⁸ Training faculty members to teach about ethical issues related to opioid prescribing, assessing the quality of teaching and student learning, and providing opportunities for students to apply what they learn would augment future physicians' capacity to more effectively respond to the opioid epidemic.

Improvement Strategies

The current state of ethical education and opioid-related courses in medical schools has proven to be ineffective in addressing the opioid epidemic. It is therefore imperative that measures be taken in order to properly equip future physicians to [appropriately prescribe opioids](#).

Multilevel interventions. Meisenberg et al found that a series of multifaceted interventions within the Anne Arundel Medical Center led to a 38% reduction in opioid overprescribing relative to the mean baseline level of prescribing.⁹ As the authors note, multilevel intervention encompasses implementing "departmental grand rounds, service meetings with data review," and "one-on-one meetings with prescribers."⁹ Although these interventions took place within health care facilities, they convey an important message: utilization of multiple modes of teaching and learning provides a better foundation for more appropriate prescribing behaviors. Translating these interventions into medical school curricula could take the form of clinically focused lessons encompassing medical simulations and case-based learning, giving students time with trained clinicians in the field and meaningful clinical exposure to real patients, and group case studies and service meetings. Increasing the clinical exposure of students while enrolled in courses in which they learn about opioid prescribing would enhance their capacity to apply their learning—for example, by identifying patients who are at greater [risk for misusing prescribed opioids](#) and by prescribing appropriately.

These proposed educational reforms are backed by qualitative findings, as a 2012 study in the *British Journal of Clinical Pharmacology* found that prescribing is a skill that requires knowledge combined with practical experience within the clinical context.¹⁰ Indeed, many physicians reported that they could not "get to grips" with prescribing after having been taught in a classroom and that they learn the most when it becomes relevant in their practice.¹⁰ Therefore, it is apparent that increased clinical exposure as a learning method would greatly enhance the preparedness of medical students.

Assessment. Improving the quality of faculty teaching and the nature and scope of student learning assessment are also crucial to preparing students to prescribe opioids appropriately. Examinations, for example, should test medical students' applied knowledge, such as their ability to write a prescription, manage pain, and deal with ethically relevant factors, including explaining conflicting responsibilities to individual

patients and the health care community and the reasons for adhering to guidelines if appropriate.¹¹ Currently, it is difficult for medical students to be properly evaluated when there are so few trained specialists in pain and addiction medicine.⁷ Training younger and enthusiastic physicians in these fields while also recruiting nurses, pharmacists, and other pharmacologists would not only increase the number of personnel available to do good cross-disciplinary assessment of students' learning⁵ but also reinforce the importance of ethical aspects of prescribing of opioids and other addictive substances.

Substance use. A 2012 study conducted by the National Center on Addiction and Substance Abuse at Columbia University found that few patients with a history of risky substance use received any form of adequate care, screening, or early intervention.¹² These results, spanning numerous patients and clinicians, reinforce the need for more robust educational experiences in addiction management. The interface of addiction and pain management presents physicians with an ethical dilemma in prescribing opioids: on the one hand, physicians are motivated to control their patients' pain well, but, on the other, they don't want to contribute to or launch a patient's addiction to opioids. This dilemma is particularly hard to manage in patients who have an opioid addiction and who also need good pain care. Implementing more courses on addiction management and helping students to recognize this dilemma would be a major step towards improving medical education about opioid prescribing.

Longitudinal curricula. A longitudinal opioid prescribing curriculum that prominently integrates ethics is vital to prescribing education. As it stands, opioid prescription training is a fairly short-term, stand-alone segment of medical education. Extending it so that it manifests at numerous points in the curriculum, however, can lead to better preparedness. In describing the development of a better prescribing curriculum, Ross and Maxwell emphasize that learning should take place within "different modules and over several years using horizontal and vertical teaching strands."¹¹ They also suggest that undergraduate medical education should focus on ethically and clinically relevant drug knowledge that can be easily applied in later years in medical training.¹¹

A current model curriculum that merits recognition exists at the University of Massachusetts Medical School. The "Opioid Conscious Curriculum" is woven into all 4 years of the educational process and involves the use of standardized patient cases along with other experiential learning.¹³ The opportunity to speak with patients with differing levels of pain, addiction status, and substance use history is an instrumental element of the curriculum.¹³ Another potentially advantageous component of the curricular setup is a framework for interdisciplinary cases involving physicians and other health care workers.¹³ The longitudinal nature of the opioid and ethical curriculum at the University of Massachusetts Medical School—combined with the numerous opportunities for simulations, clinical exposure, and interdisciplinary learning—is, we

believe, a monumental step forward in prescribing education. Such steps should be promoted at other medical schools.

Conclusion

Currently, medical education about the ethical dimensions of opioid prescribing lacks clarity, consistency, and structure. Opioid-related education is being acknowledged as an important topic, but its adoption in many schools is impeded by a lack of experienced faculty and good strategies for assessing students' learning. Medical students will be better prepared to deal with the ethical implications of opioid prescribing when steps are taken along the lines of those we've suggested here.

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AMA CODE SAYS

AMA *Code of Medical Ethics*' Opinions Related to Prescription Drugs

Rachel F. Harbut and Danielle Hahn Chaet, MSB

Abstract

The AMA *Code of Medical Ethics* offers guidance on topics related to prescription drugs, including access, stewardship, and professionalism.

Physicians' traditional role as [stewards of limited health care resources](#) is being reinterpreted in terms of their relationships with key players in the health care sector. While physicians still assess risks and benefits when prescribing medications for patients, rising drug prices,¹ formulary restrictions, and quantity limitations² introduce new complications to stewardship decisions. Physicians must not only prescribe clinically appropriate treatments but also coordinate³ and advocate⁴ for patients' access to needed interventions. Additionally, multidisciplinary care teams, necessitated in part by an expanding pharmacopeia and growing demands for access to quality health care, introduce new fields of expertise to clinical encounters. The American Medical Association (AMA) *Code of Medical Ethics* offers guidance to physicians making care plans with colleagues and offering treatment recommendations to patients that are relevant to physicians' stewardship role.

Availability of services and benefits covered by patients' insurance plans, for example, can influence clinical judgment.⁵ Opinion 11.2.1, "Professionalism in Health Care Systems," states:

Structures that influence where and by whom care is delivered—such as accountable care organizations, group practices, health maintenance organizations, and other entities that may emerge in the future—can affect patients' choices, the patient-physician relationship, and physicians' relationships with fellow health care professionals.⁶

Opinion 11.1.2, "Physician Stewardship of Health Care Resources," also recommends that physicians "be transparent about alternatives, including disclosing when resource constraints play a role in decision making."⁷ Opinion 11.1.2 states that *individual* physicians "cannot and should not be expected to address the systemic challenges of wisely managing health care resources,"⁷ and offers recommendations for medicine as a *profession* to address systemic inequity. Opinion 11.2.4, "Transparency in Health Care," specifically suggests that physicians collectively advocate for transparency of health plans with which they contract to help reduce external entities' influence on clinical judgment and promote all patients' access to needed care.⁸ Examples of other policies

and practices that promote these goals could include making formularies that list numerous affordable interventions, implementing billing practices that promote [cost transparency](#), and ensuring compliance with federal insurance regulations.

Opinion 11.1.4, “Financial Barriers to Health Care Access,” states that “physicians individually and collectively have an ethical responsibility to ensure that all persons have access to needed care regardless of their economic means.”⁹ Recommendations include urging physicians to connect patients, when needed, with public or charitable programs that offer resources and support to patients. Opinion 11.2.3, “Contracts to Deliver Health Care Services,” advises physicians to endorse agreements that minimize conflicts of interest, avoid “mechanisms intended to influence physicians’ treatment recommendations,” and support “advocacy on behalf of individual patients.”¹⁰

The AMA *Code* opinions discussed here recognize the challenges physicians face when striving to exercise their best clinical judgment for patients, especially given systemic inequities that limit some patients’ access to needed interventions. They also serve as reminders of physicians’ professional responsibilities to [advocate for individual patients](#) and, collectively, to advocate for policies that motivate health equity.

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STATE OF THE ART AND SCIENCE

Evolving Medicaid Coverage Policy and Rebates

Jennifer A. Ohn, MPH and Anna Kaltenboeck, MA

Abstract

Medicaid covers approximately 1 in 5 Americans and accounts for one-sixth of US health care spending. Despite having to navigate increasing and variable spending on prescription drugs, Medicaid programs must balance their annual budgets, and they rely heavily on the Medicaid Drug Rebate Program (MDRP). The MDRP requires programs to maintain an open formulary covering all of a manufacturer's drugs in exchange for being given the lowest price in the market. Recent attempts by states to close their formularies signal that the benefit of this program might be attenuated by the lack of negotiating leverage in the rest of the market, exposing Medicaid to higher prices. Regardless of whether closed formularies would succeed in constraining Medicaid prescription drug spending, this trend raises important questions about the usefulness of a system that pegs Medicaid drug spending to net prices negotiated by others in the market.

Medicaid Beneficiaries and Formularies

Medicaid programs, collectively, constitute the largest US public payer, covering 21% of the population and accounting for one-sixth of total US health care spending.^{1,2} Compared with other payers, Medicaid serves a more vulnerable population, including low-income Americans and those who are unable to work due to a disability or medical condition. Many Medicaid beneficiaries are ineligible for employer-sponsored health insurance or are unable to afford plans offered by exchanges. Medicaid also plays a critical role in addressing public health concerns, such as substance use disorders and infectious diseases, including Hepatitis C and HIV/AIDS. In 2016, Medicaid programs spent \$9.4 billion on HIV/AIDS, making it the second largest public funder for all HIV/AIDS related care.³

Although coverage of prescription drugs under Medicaid is optional, all states have opted in,⁴ and, for all states, spending on prescription drugs presents a significant and growing line item in their budgets. In 2016, Medicaid spent \$60.5 billion on prescription drugs before rebates or discounts.⁵ Although Medicaid enrollment growth is projected to slow, prescription drug spending is expected to continue placing fiscal demands on states.^{1,5,6,7} To defray some of these costs, state governments must comply with conditions of the

federal Medicaid Drug Rebate Program (MDRP), a cornerstone of which is a requirement to have an open formulary in exchange for rebate payments from manufacturers.

The alternative to an open formulary is a closed formulary, a design already adopted by other health plan types. A closed formulary allows plans to exclude drugs from coverage, increasing their ability to negotiate for discounts and rebates. The Veterans Health Administration (VHA), for example, has maintained a national formulary—which includes closed drug classes—since 1997.⁸ *Closed* in this instance means that VHA facilities are prohibited from including on their formularies any drugs excluded from the national formulary. Some exceptions aside, drugs can also be excluded from Medicare Part D formularies, a deliberate policy choice intended to give health plans leverage to negotiate for lower prices.⁹ In commercial plans of health maintenance organizations, 71% of members were subject to closed formularies in 2015,¹⁰ and some research suggests further opportunities for savings in classes of drugs that have remained open.^{11,12} An open formulary requirement is one that is unique to the Medicaid program.

Here we describe the MDRP and examine efforts by Medicaid programs to contain drug costs, including closed formularies and waivers.

Rebates and the Medicaid Drug Rebate Program

Instituted under the Omnibus Budget Reconciliation Act of 1990, the MDRP extends manufacturer rebates to Medicaid programs for drugs used by beneficiaries enrolled in fee-for-service and managed care programs. To qualify for these rebates, Medicaid programs must cover all of a manufacturer's Food and Drug Administration (FDA)-approved drugs, with few exceptions.¹³ Rebate payments are shared between the federal and state governments and amounted to approximately \$31 billion in 2016.⁷ Manufacturers' participation in the MDRP is a condition of having their products covered under Medicaid.

MDRP rebate payments are calculated based on 2 main formulas. For single-source or innovator (brand-name) drugs, the rebate is the greater of (1) a statutory discount (23.1%)¹⁴ off the average manufacturer's price (AMP), which is the average net price at which the manufacturer sells to wholesalers and pharmacies, or (2) the difference between a drug's AMP and the best price (or the lowest price) for that drug in the market. For generic drugs that come from multiple sources, the discount is 13% off the AMP.¹⁵ These discounts are provided in the form of rebate payments by the manufacturer to the Centers for Medicare and Medicaid Services (CMS). CMS also applies a Consumer Price Index penalty for drug price increases beyond the inflation-adjusted price. If price increases for a given drug exceed inflation, a penalty sum is added to the rebate payment¹⁵; this penalty sometimes results in generic drugs being more expensive than older brand-name drugs.

MDRP rebate amounts vary by drug depending on the negotiating power of Medicare Part D and commercial health plans, which determines whether the best price of a brand-name drug falls above or below the statutory minimum discount of 23.1% for Medicaid. Brand-name drugs with many competitors often require significant net price concessions to pharmacy benefit managers and health plans in order to gain favorable coverage; these concessions benefit Medicaid when drugs' net prices fall well below the 23.1% statutory minimum discount for brand-name drugs. However, payers are often unable to negotiate lower net prices for those brand-name drugs with few therapeutic alternatives, strong consumer demand, or coverage requirements that shield them from utilization management or access restrictions. In these cases, Medicaid plans are more likely to obtain the 23.1% rebate level.^{6,16} The barrier to negotiation is particularly common for brand-name specialty drugs, which, in 2017, accounted for \$9.8 of \$12 billion in US net spending growth on new brand-name drugs.¹⁷ Brand-name [drugs used to treat cancers](#), hepatitis C, HIV/AIDS, and multiple sclerosis were major drivers of this spending. Drugs for hepatitis C and HIV/AIDS constitute a disproportionately large share of Medicaid prescription drug spending,¹⁸ and their increased budget impact has amplified the need to protect vulnerable patients while also forcing difficult trade-off decisions for Medicaid programs.

Cost Containment

The MDRP requires states to cover all of a manufacturer's FDA-approved drugs, with a few exceptions, regardless of their cost or performance relative to other options, and this is a vulnerability for Medicaid programs. Currently, states' primary means of persuading manufacturers to offer greater net price concessions is their preferred drug list (PDL).⁶ PDLs include drugs for which manufacturers offer supplemental rebates beyond those offered by the MDRP and are primarily enforced through utilization management tools that seek to control prescription drug use by patients. Utilization management could require beneficiaries to gain prior authorization, comply with step edits, and navigate refill limits.¹⁹ These kinds of requirements are not without their drawbacks: one study found that between 47% and 79% of Medicaid beneficiaries were subject to these [cost-containment](#) utilization management tools and that 22% have experienced compromised access to needed medications.⁴ Introduction of high-cost treatments for hepatitis C, for example, compelled Medicaid programs struggling to protect their budgets to draw on these tools. More than half of states have instituted prior authorization requirements conditioned on patients' liver fibrosis scores, although some of these requirements have not survived challenges in federal courts.²⁰

Pressure to contain rising drug spending, particularly for drugs in classes that have been protected from competition and net price erosion, has prompted states to seek new approaches to administering Medicaid drug benefits. For example, some states participate in purchasing collectives, which help them negotiate net price concessions from manufacturers.²¹ Some also rely on managed care programs to negotiate with

manufacturers and administer their prescription drug benefit by including in their capitation amounts for prescription and outpatient drugs.²² New York has implemented a spending cap that allows the state's Medicaid program to negotiate for additional rebates for specific drugs if overall drug spending exceeds a pre-determined growth target.²³ This spending cap was first enforced when determining coverage for a cystic fibrosis drug, lumacaftor/ivacaftor. In 2018, New York negotiated with this drug's manufacturer an annual price of \$83 000, down from the \$250 000 per year list price.^{24,25}

More ambitious efforts by state Medicaid programs to contain drug costs, such as [closed formularies](#), stand at odds with open formulary provisions of the MDRP and require a federal waiver to implement.

Waivers and Closed Formularies

A closed formulary would allow a Medicaid program to decline to cover certain drugs, increasing its negotiating leverage and containing costs. In effect, programs could wield the threat of exclusion to gain greater net price concessions from manufacturers. Closed formularies have been adopted by Express Scripts (ESI) and CVS,²⁶ which administer drug benefits of commercial health insurance and Medicare Part D plans. These companies' formularies are substantially more restrictive than current Medicaid plans' drug benefits; in the 2016 fiscal year, 20% of drugs covered in Massachusetts's Medicaid plans were not covered either by CVS or ESI formularies or by both.²⁷

Closed Medicaid formularies are not unprecedented. Before the start of the MDRP, 19 of 47 state Medicaid programs then in operation adopted a restricted (closed) formulary design with drugs selected by state agencies on the basis of cost or efficacy.²⁸ Excluded drugs included growth hormones such as somatrem, isotretinoin, and a selection of branded nonsteroidal anti-inflammatory drugs.²⁹ A review of studies from this era found that these states' Medicaid plans incurred modest savings from these restrictions.²⁸ However, past experience is unlikely to be informative, as federal pricing and reimbursement policies have changed substantially since this period.

Medicaid programs' attempts at exclusionary approaches to formulary design have met with mixed enthusiasm at the federal level. Massachusetts, a state with a history of pioneering health care policy choices (one example being the establishment of the Massachusetts Health Connector, on which the Affordable Care Act health insurance exchange was modeled), applied for a Section 1115 waiver (a request to waive the MDRP requirement to have an open formulary) from CMS and proposed to close its Medicaid formulary, restricting coverage such that at least one drug in every therapeutic class would be covered.³⁰ CMS rejected the waiver request, reaffirming in its official announcement that, unless Massachusetts chose to forgo MDRP rebates altogether, all drugs produced by manufacturers participating in the MDRP must be covered by Medicaid. Despite this rejection, the President's budget request for fiscal year 2019

called for up to 5 states to pursue demonstration projects that address high costs of prescription drugs via closed Medicaid formularies.³¹

Leverage and Vulnerable Patients' Drug Needs

Manufacturers often rely on high list prices to give them headroom to offer discounts and rebates to Medicare Part D and commercial plans in exchange for their formulary preference. The MDRP leaves Medicaid programs reliant on rebates that depend heavily on decisions and actions taken by commercial and Medicare Part D health plans, which determine whether net prices of brand-name drugs fall below the minimum 23.1% discount guaranteed to Medicaid. The MDRP thus established a way to ensure that Medicaid programs had access to the same, or better, net prices negotiated by these other entities. Although the statutory rebate has protected Medicaid programs from the growing differences between list and net prices in some drug classes, the program is less effective at addressing expenditures on drugs with minimal rebates, such as those used to treat cancers and HIV/AIDS. As spending among drugs with lower rebates continues to grow, MDRP payments might no longer suffice to subsidize their use.

Medicaid programs' ambition to experiment with closed formularies arose after the rest of the market had already begun to incorporate this mechanism. Although it seems likely that this approach has afforded health plans more negotiating power to obtain net price concessions in competitive classes of drugs, which would be passed through to Medicaid, whether and to what extent it has improved their ability to lower costs for drugs with minimal rebates, for which there is high demand and coverage protections, is unclear. The uncertain success of closed formularies raises a question about whether Medicaid could improve on that performance. There are no safeguards in place to ensure that these same tools do not increase Medicaid spending. For example, it is possible that using more aggressive management strategies, such as closed formularies, reduces access to some drugs and amplifies financial burden on patients with commercial, health exchange, or Part D plans that rely on closed formularies, increasing the likelihood that they will become eligible for Medicaid.

Conclusion

The design of the MDRP program has left Medicaid programs exposed to the consequences of access and pricing decisions by others in the market, including other payers, pharmacy benefit managers, and manufacturers. While this approach leverages the negotiating power of other payers in competitive classes of drugs, it fails to benefit Medicaid programs when commercial negotiating leverage falls short. In the near term, economic benefits to states with closed Medicaid formularies would likely depend on whether increases in list prices for drugs with lower rebates exceeds reductions in net prices for those drugs that do offer substantial concessions to commercial and Medicare Part D plans.

Regardless of whether or how they are implemented, closed formularies signal a deeper market challenge for brand-name drugs and reflect evolving demands on policies that aim to protect Medicaid by leveraging other payers. In addition to concerns about access restrictions for the most vulnerable patient populations, debate over closed formularies raises broader questions about the usefulness of commercially negotiated rebates as a strategy for controlling costs and the effects on Medicaid of escalating payer restrictions in other parts of the market. Policymakers might find benefit in revisiting the assumptions underlying the program and in exploring other options to secure a more predictable and constrained pattern in Medicaid prescription drug spending.

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STATE OF THE ART AND SCIENCE

Are Medicaid Closed Formularies Unethical?

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Abstract

State Medicaid programs have proposed closed formularies to limit spending on drugs. Closed formularies can be justified when they enable spending on other socially valuable aims. However, it is still necessary to justify guidelines informing formulary design, which can be done through a process of decision making that includes the public. This article examines criticisms that Medicaid closed formularies limit deliberation about decisions that affect drug access and unfairly disadvantage poor patients. Although unfairness to poor patients is a risk, it is not a problem unique to Medicaid, since private insurance programs have also implemented closed formularies.

Closed Formularies

As health care costs increase, state Medicaid programs are looking for ways to limit spending. In 2017, both Massachusetts and Arizona submitted waiver requests to the Centers for Medicare and Medicaid Services (CMS) for closed Medicaid formularies that would allow them to select drugs for coverage based on price and effectiveness rather than providing, as is currently required, all drugs covered by the CMS Medicaid Drug Rebate Program, which includes nearly all new US Food and Drug Administration (FDA)-approved drugs.^{1,2,3} Because all government programs must pay for the public goods and services they provide out of finite budgets, access to health care services for Medicaid enrollees must be balanced against other social goals that public resources could support. Massachusetts and Arizona saw closed formularies as one way of achieving this balance, although some drug manufacturers and patient organizations have criticized the Massachusetts policy as unfairly limiting treatment options.³

How can [closed formularies](#) achieve ethical acceptability? We argue in the first section that a minimum ethical requirement for a closed formulary is that savings be put to socially valuable uses. Once that condition is met, 2 ethical issues remain: (1) Which values and procedures inform access choices? (2) Do closed formularies unfairly disadvantage poor patients? In response to the first question, the next section argues that policymakers who propose closed formularies should consider a broader range of social values and discuss procedural approaches for making drug inclusion decisions. In response to the second question, the concluding section argues that even if a Medicaid

closed formulary is less generous than private formularies, it is not necessarily unjust. In sum, rather than rejecting closed formularies outright, we argue that policymakers should apply ethical principles in considering whether and how to implement closed formularies.

Social Values and the Ethics of Saying No

A closed formulary enables a payer to say no to some pharmaceuticals. Specifically, the payer has the power to say no both to pharmaceutical firms selling a given drug and to patients who would like that drug. Saying no can enable savings both directly and indirectly. Directly, it can reduce or eliminate spending on costly drugs whose benefits either do not exceed those of cheaper alternatives or do not justify their costs. Indirectly, it can enable payers to negotiate more effectively with pharmaceutical firms by allowing payers to credibly threaten to refuse to pay high prices.³

Both saying no to firms and saying no to patients present ethical issues. But saying no to firms presents ethical issues only indirectly—saying no to a drug signals that firms should lower prices (in the short term) or refocus their research and development efforts on other drugs or drug classes (in the longer term). In contrast, saying no to patients directly presents ethical issues, because doing so—depending on what other options are available—can limit patients' treatment options and potentially the quality and length of their lives. Norman Daniels has famously argued that the structure of the United States health care system makes saying no difficult to justify, because the savings from saying no to some patients could end up serving socially unproductive purposes.⁴

The first step in justifying a closed formulary, therefore, is to explain how the savings from the closed formulary will be used. The more socially valuable the purpose, the easier a closed formulary is to justify. What it means for a purpose to be socially valuable is, of course, debatable. Many things other than health care—early childhood education or even direct cash transfers—can promote health,⁵ and, in any event, social value encompasses more than health promotion. Similarly, social value encompasses more than the interests of current beneficiaries. Social programs like Medicaid are justified by their contribution to the common good and are not the private property of current beneficiaries. Although current beneficiaries should not be given veto power over formulary restructuring, decisions about formulary design should include their perspectives, as we argue next.

Deliberative Procedures and Public Decisions

Assuming the savings from a closed formulary are used for socially valuable purposes, the question becomes what drugs to include and how to make these decisions, which can involve numerous ethical considerations. Although the goal of a closed formulary—reduced spending on drugs—implies an emphasis on cheaper alternatives, other goals such as improving effectiveness or benefiting the least advantaged are also relevant.

The recent Massachusetts proposal for a CMS waiver, mentioned earlier, illustrates the need for clarity about values or reasons informing formulary design. In 2017, Massachusetts submitted a Medicaid 1115 waiver request for the Medicaid program, MassHealth,² which CMS rejected in 2018.⁶ Among the proposed changes to MassHealth was the introduction of a closed formulary with the explicit intention of reducing overall spending on drugs. There were 2 requirements for the formulary: (1) at least one drug per therapeutic class would be included and (2) for each drug included there should be adequate evidence demonstrating its effectiveness.² Arizona submitted a similar proposal, which CMS has not yet decided on,⁷ although the Arizona Health Care Cost Containment System suggested 2 drugs per therapeutic class would be covered unless one is "clinically superior."¹ Both waivers claim that access to medically necessary care will be maintained since minimum access across therapeutic classes is required. Including at least one drug per class is also a politically smart move that avoids excluding patient groups. However, this requirement might conflict with the goal of reduced spending and the further requirement that included drugs have demonstrated effectiveness. Recently approved drugs, such as eteplirsen for Duchenne muscular dystrophy or nivolumab for some cancers, are [new classes of drugs](#) with limited evidence and very high costs.^{8,9} Including these drugs in the closed formulary goes against its 2 aims of reducing costs and encouraging the use of more effective drugs.

Although the one-drug-per class requirement is an easy position to take, policymakers should consider the intention of the closed formulary and the principles that guide it, its alignment with the overall program goals of Medicaid, and enrollees' values. Aiming merely to reduce costs by including only the cheapest drugs would unjustifiably ignore other relevant considerations; it also matters which drug has the greatest effect, is most effective for the greatest number of people, or best treats those who are sickest. There are many possible factors that could inform formulary design, and sometimes they will conflict. For example, the decision of whether to include a cancer drug like nivolumab in a closed formulary should require weighing a number of factors including cost, strength of evidence of effect, and the burdens experienced by patients in the final stages of cancer. People will, of course, disagree about which of these factors is most important or socially valuable and therefore justifies [exclusion of a drug](#) from the formulary.

To address the problem of conflicting values in setting limits on drugs to be included in a closed formulary, policymakers could turn to procedures that involve citizens and that are transparent. This next step presupposes that it is not enough to justify decisions about which drugs to include in a closed formulary because these choices enable socially valuable purposes; the process of making the decision about how to save money also matters. Daniels has proposed a procedure, called accountability for reasonableness, specifically to address the problem of insurers that limit health care access.¹⁰ Accountability for reasonableness requires that these limit-setting decisions and the

reasons for them be publicly available, be based on trade-offs and reasoning that the public served by the plans will find appropriate, and include an appeals process.¹⁰ Medicaid, as an institution serving the public, should use high standards of deliberation, public engagement, and transparency for its decisions.

Oregon implemented such a deliberative process for [reforming its Medicaid program](#) in the early 1990s. In order to reduce costs and extend coverage, state health planners created a ranked list of services that would be provided. The initial list, based only on cost-effectiveness calculations, resulted in coverage trade-offs considered unacceptable by the public, with minor ailments prioritized over life-threatening conditions.¹¹ A public consultation process gathered values that informed the final ranking, which continues to be updated.^{11,12,13} Although Oregon conducted a state-wide public discussion of limit-setting values, deliberation could also occur on a small scale. The Choosing Healthplans All Together (CHAT) exercise has been run in multiple settings with lay participants who have private and public insurance plans and draws out people's preferences for health care access—preferences that shift when they consider population needs rather than their own.¹⁴ These sorts of public and deliberative exercises engage people in important public policy decisions, which ensures the legitimacy of the results and increases the likelihood of their acceptance.

The MassHealth and Arizona closed formulary proposals should have considered—and future ones should consider—the example of public, deliberative procedures to inform decisions about which drugs to include in closed formularies. The process must include both the Medicaid beneficiaries and the broader public, who are the payers and have interests in how the funding serves the public good within the state.

Fairness and Singling Out Poor Patients

In addition to considering the values and processes used in formulary construction, it is worth considering whether applying closed formularies selectively to Medicaid beneficiaries would be unfair, as some have charged.¹⁵ Proposed limits—for instance, on sugar-sweetened beverages in food assistance programs—have been criticized.¹⁶ But the charge of singling out poor patients does not apply particularly well to the use of closed formularies in Medicaid programs because other public payers as well as private payers use closed formularies.³

Although the use of closed formularies is not distinctive to programs serving poor patients, specific formulary designs could be. Hypothetically, would it be fair for Medicaid closed formularies to include drugs that are cheaper but less effective than the drugs included in other closed formularies? This would conflict with the view—endorsed by 75% of US adults in a 2003 poll—that quality of health care should not depend on wealth.¹⁷ Such a proposal presents the question of whether poorer patients are owed equal access to specific pharmaceuticals rather than a decent minimum. In an article on

global health, one of us (G.P.) has argued that opting for cheaper treatments can enable more patients to receive treatments.¹⁸ However, tailoring formulary designs to include more effective treatments is likely to be less controversial than tailoring them to reduce costs. For instance, given that medication access might contribute to adherence challenges that Medicaid patients can face,¹⁹ a closed Medicaid formulary could try to include drugs that make adherence easier for people in resource-limited circumstances.

The potential for closed formularies to uniquely disadvantage poor patients is not alone reason enough to reject closed formularies in government programs. Arguments in this article—that there should be a minimum ethical requirement for justifying the reallocation of funds and that the formulary design should be guided by a procedural approach emphasizing deliberation, transparency, and engagement—do not dismiss the idea of closed formularies but rather suggest how they might be achievable in a socially just way.

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POLICY FORUM: PEER-REVIEWED ARTICLE

Should a Law Governing the Pharmaceutical Market Be Ethically Examined Based on Its Intent or Its Practical Applications?

Jordan M. Warchol, MD, MPH

To claim one AMA PRA Category 1 Credit™ for the CME activity associated with this article, you must do the following: (1) read this article in its entirety, (2) answer at least 80 percent of the quiz questions correctly, and (3) complete an evaluation. The quiz, evaluation, and form for claiming AMA PRA Category 1 Credit™ are available through the [AMA Ed Hub™](#).

Abstract

Prescription drug prices are a top health care concern among US consumers. Although this issue is at the forefront of current policy discussions, it is not new. In 1984, the Drug Pricing Competition and Patent Term Restoration Act (colloquially, the Hatch-Waxman Act) addressed drug pricing concerns. This article argues that Hatch-Waxman properly applies utilitarian principles to complex issues of biopharmaceutical development by balancing innovation and availability. However, the statute's efficacy has been marred by so-called pay-for-delay arrangements, which disrupted that carefully constructed equilibrium. This article also argues that the 2013 US Supreme Court holding in *Federal Trade Commission v Actavis, Inc* appropriately restored the utilitarian balance initially achieved by Hatch-Waxman.

Ethical Implications of Pharmaceutical Policy Design and Application

Prescription medication cost is a top health care priority for nearly two-thirds of Americans.¹ For example, insulin prices continue to increase,² making it difficult for patients to comply with medication regimens, which in turn can lead to disease complications and increased costs.³ In response to constituents' concerns, Congressional leaders have attempted to find solutions to the problem.⁴

Thirty-five years ago, the Drug Price Competition and Patent Term Restoration Act of 1984,⁵ known as the Hatch-Waxman Act, was created to increase the number of available generic medications and decrease prices through competition. Under Hatch-Waxman, brand-name manufacturers' profits are protected for a period of time when no competitors of the drug will be approved by the US Food and Drug Administration (FDA). This exclusivity period is in addition to the term of any patents on the drug but runs concurrently. Generic manufacturers also benefit from the law due to its establishment

of an [alternate pathway for generics](#) to come to market. Instead of undertaking large, expensive clinical trials to prove safety and efficacy, a generic manufacturer must show only that the generic medication achieves bioequivalence.⁶ Generic manufacturers also have a process by which they can challenge the patent protections on a brand-name medication, potentially bringing their product to market earlier than would otherwise be allowed.⁵

Since Hatch Waxman's adoption, significant growth in the generic market has occurred; 89% of prescriptions written in the United States are currently filled with off-brand drugs.⁷ Brand-name manufacturers have continued to develop innovative medications for a multitude of illnesses, including terminal genetic conditions⁸ and refractory cancers.⁹ The concurrent expansion of these competing industries underscores the balance struck by Hatch-Waxman between the need for pharmaceutical advances and the need to make those advances widely accessible.

This article will first examine the ethics of the law's design through the prism of utilitarianism. It will then turn to pay-for-delay settlements, wherein a brand-name company pays a generic company to keep the generic medication off the market, which challenge the ethical intent of Hatch-Waxman by circumventing the utilitarian principles underlying the law. An analysis of the US Supreme Court decision in *Federal Trade Commission v Actavis, Inc* will further examine such settlements.

Background of the Hatch-Waxman Act

When a brand-name manufacturer wants to bring a new drug to market, it must submit a new drug application, which is reviewed by the FDA before approval for sale.¹⁰ It is estimated that the process of bringing a drug to market costs hundreds of millions to billions of dollars.^{11,12} The capital used to fund this research and development is recouped through market exclusivity, a purposeful [monopoly](#) designed as an enticement to brand-name manufacturers to undertake the risky drug development process.¹³

Following a pioneer drug's period of exclusivity, generic drug makers can file an abbreviated new drug application (ANDA), which has less stringent thresholds for drug approval.⁵ In filing the ANDA, generic companies can attempt to enter the market before the expiration of the brand-name company's patent term(s) by certifying that their product does not infringe upon any patents held by the brand-name manufacturer or that any patent infringed upon is invalid; this is known as a Paragraph IV certification.⁵ Although the generic is certifying that it has not violated any of the brand-name company's patents, the statutory language of Hatch-Waxman deems a Paragraph IV certification an act of patent infringement in itself, allowing the brand-name company to bring legal action against the generic company. Historically, Paragraph IV disputes that have proceeded to judicial decision have generally been found in the generic manufacturer's favor.¹⁴

Utilitarian Principles Underlying Hatch-Waxman

Utilitarianism, according to J. S. Mill, follows the “Greatest Happiness Principle, [which] holds that actions are right in proportion as they tend to promote happiness, wrong as they tend to produce the reverse of happiness.”¹⁵ On contemplating the utility of a choice, it is not merely the happiness of the decider that must be considered but the happiness of all who will be affected by the decision; the ethical choice is that which maximizes this happiness. Some modern utilitarian thinkers have argued that it is not only happiness but also well-being that must be maximized.¹⁵ In any case, utilitarianism relies wholly on the ethical tenet of utility to decide the morality of a choice.¹⁶

Hatch-Waxman exemplifies the application of utilitarianism by a government that is representative of the myriad entities it serves because it seeks to optimize positive outcomes for all involved stakeholders. This goal is accomplished through consideration of the many complexities of the biopharmaceutical industry and its impact: the for-profit nature of pharmaceutical companies that contribute to economic growth; society’s desire for continued advances in the field of medicine; the cost of medications and the societal consequences of those costs, including medication nonadherence and its own costs; and the societal and economic contributions of patients whose conditions are improved by such medications. The ripple effects of the pharmaceutical industry are wide and various. Accordingly, Hatch-Waxman aims to balance stakeholders’ various interests.

Some might contend that the application of utilitarian principles by government is inappropriate. One charge is that utilitarianism is based on subjective preferences, allowing otherwise immoral ideas to be considered as benefits based on an individual’s satisfaction.¹⁶ Others critical of the legislation could point to the apparent injustice of utilitarian theory, which can promote the majority’s interests over those of the minority.¹⁵ According to Beauchamp and Childress, “injustice involves a wrongful act or omission that denies people resources or protections to which they have a right.”¹⁶ Under utilitarianism, any act would be classified as “wrongful” that does not promote the highest utility, and utility must be considered relative to all entities to which the policy applies. Under Hatch-Waxman, utility is maximized through careful balancing of the competing interests of multiple stakeholders without depriving others of their rights. The questions of injustice and what is “wrongful” become more complex in examining the current environment of Hatch-Waxman.

Emerging Legal Challenges

Since it was enacted, Hatch-Waxman has been tarnished by legal maneuvers that comply with the letter of the law but undermine its intent. One such tactic, known as [pay for delay](#), occurs when a reverse settlement is reached between brand-name and generic manufacturers regarding Paragraph IV litigation. This arrangement is unique because of the terms of the settlement agreement. Whereas a typical patent dispute settlement results in the infringer paying the infringed, in a pay-for-delay settlement,

the infringing brand-name company pays the infringing generic company. In exchange, the generic company agrees not to bring to market its product until a later time. These agreements typically occur during Paragraph IV litigations, after the generic manufacturer has been sued for patent infringement by the brand-name manufacturer as a way for the brand-name manufacturer to avoid judicial opinions. The Federal Trade Commission (FTC) has declared such pay-for-delay arrangements violations of antitrust laws.¹⁷

The antitrust infringement question posed by pay-for-delay arrangements was addressed by the US Supreme Court in *Federal Trade Commission v Actavis, Inc*, in which a pay-for-delay settlement between Actavis and Solvay Pharmaceuticals was at issue.¹⁸ The agreement stipulated that Actavis would delay its generic's entry into the market for 9 years and serve as a marketing arm for the brand-name drug. In return, Solvay would pay Actavis a substantial sum of money,¹⁸ presumably much larger than the value of the marketing provided by Actavis. This agreement was upheld by the Eleventh Circuit Court of Appeals, which ruled that the anticompetitive effects of the pay-for-delay settlement were within the exclusionary potential of the patent that was under Paragraph IV challenge and that therefore the settlement did not violate antitrust laws.¹⁸

The Supreme Court reversed the lower court's ruling against the FTC, holding that reverse payment settlements could sometimes violate antitrust laws, depending on the conditions of the settlement. Consequently, any pay-for-delay settlement must be evaluated according to 5 conditions: the effects on competition; the justified or unjustified nature of the consequences of the agreement; the strength of the brand-name company's incentive to keep a generic out of the market; the perceived strength of the original patent that the generic company was contesting; and the rationale of the settlement.¹⁸

Actavis underscores the role of utilitarianism in government. In *Actavis*, the Supreme Court held that the collective ratio of benefit to harm was not maximized by the settlement.¹⁸ Specifically, in *Actavis*, the court applied *act utilitarian* principles, wherein utility must be examined independently for each case under the specific set of circumstances that define it.¹⁷

One of the major criticisms of act utilitarianism is that case-by-case determinations of utility can result in the waiving of rules that would otherwise uphold the moral standard,¹⁷ which could result in scenarios wherein an otherwise immoral act would be seen to result in the most utility. However, in the evaluation of pay-for-delay settlements under Hatch-Waxman, the application of act utilitarian standards to an antitrust question is arguably the best answer. US antitrust statutes are intended to protect citizens from competitive monopolies and collective harm.¹⁹ If the particulars of a settlement agreement are not examined, it cannot be determined if it would result in harm. A blanket application of antitrust law, such as would be applied under *rule*

utilitarian principles, could have grave consequences. Take, for example, a case similar to that of *Actavis*: a brand-name manufacturer pays a generic manufacturer a sum of money, and, in exchange, the generic manufacturer takes over the marketing of the brand-name drug and agrees to delay the generic's entry into the market. Further imagine that, unlike in *Actavis*, the brand-name company no longer has the resources to adequately market the drug, which is why the marketing is being outsourced. Without the agreement, the brand-name company would no longer market the drug, which could decrease its use and decrease societal benefit. While not typical of pay-for-delay arrangements, this agreement—if it was not evaluated independently and was determined to be in breach of antitrust law simply because it was a reverse payment—could result in greater harm from inadequate marketing than from keeping the generic out of the market.

Furthermore, application of act utilitarian principles to pay-for-delay settlements entails acceptance of flexibility as societal norms change. Generally, if a court rules on a matter, that ruling must be applied to a similar legal question under that court's jurisdiction unless another case with the same question is brought forward.^{20,21} Through its opinion in *Actavis*, which required that a set of conditions be applied to a pay-for-delay settlement, the Supreme Court built in a mechanism for future rulings on similar cases to take into consideration the natural changing of cultural perceptions of benefits and harms. The calculation of utility must be responsive to the ebb and flow of social norms.

Conclusion

When writing or interpreting policy, agents of government must maximize utility for all stakeholders both at the current moment and into the future. Legislation such as Hatch-Waxman, which balances the various needs of involved parties, is necessary to achieve this mission. Equally important is the role of the judiciary branch in preserving the equilibrium between innovation and competition as new, potentially destabilizing legal challenges emerge. While concerns over drug pricing continue to swirl, policymakers must consider the delicate balance between innovation and competition. Whatever solutions might be proposed, the greatest good for the greatest number must be paramount.

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POLICY FORUM

Why Are Biosimilars Not Living up to Their Promise in the US?

Mike Z. Zhai, Ameet Sarpatwari, JD, PhD, and Aaron S. Kesselheim, MD, JD, MPH

Abstract

Biologics are among the most expensive prescription drugs in the United States, posing significant barriers to patient access to necessary treatments. An abbreviated approval pathway for biosimilars, near-identical versions of biologics made by different manufacturers, was created by Congress in 2010 to stimulate competition in hopes of driving down costs and expanding access. However, as of February 2019, only 17 biosimilars have been approved, with only 7 currently on the market. Of the few biosimilars currently available to patients, overall utilization has been limited. This article examines the current landscape of the biosimilar market, characterizes tactics employed by biologics manufacturers to delay market entry and deter prescribing of biosimilars, and assesses ethical issues related to increasing the adoption of biosimilars.

Expensive Biologics

Biologic drugs, which include therapeutic proteins and monoclonal antibodies, are large complex molecules typically manufactured in genetically engineered organisms, such as modified bacteria.¹ Biologics can be remarkably effective in treating a variety of illnesses, ranging from autoimmune diseases to cancer, but their high prices—often in excess of \$100 000 per patient per year—have driven persistent growth in prescription drug spending.¹ In the United States, biologics account for 38% to 40% of all pharmaceutical spending,^{2,3} but fewer than 2% of Americans use them.² From 2010 to 2015, biologics represented 70% of the growth in US drug spending.^{2,3}

One proposed solution to address the high cost of biologics was to facilitate the introduction of competitor products (called biosimilars) that are nearly identical to older, off-patent biologics via an abbreviated approval pathway. A similar pathway for generic small-molecule drugs had been created by the 1984 [Hatch-Waxman Act](#)⁴ and proved successful. Generic drugs now account for about 90% of all dispensed prescriptions in the United States and have saved the health care system roughly 1 trillion dollars between 2002 and 2011.^{5,6} Accordingly, in 2010, Congress passed the Biologics Price Competition and Innovation Act (BPCIA), modeled loosely on the Hatch-Waxman Act, as part of the Affordable Care Act, thereby establishing an abbreviated pathway for biosimilars to gain

approval by the US Food and Drug Administration (FDA).⁷ In this article, we characterize key clinical, economic, and ethical issues related to the approval and use of biosimilars.

What Are Biosimilars?

Under the BPCIA, the FDA might approve a biosimilar upon a manufacturer's showing that it is "highly similar" to the reference biologic and has no "clinically meaningful differences" with respect to its safety, purity, and potency,⁷ eliminating the need for the biosimilar manufacturer to conduct a full set of pre-approval clinical trials, which were required for the originator drug. Additionally, the BPCIA specifies that a biosimilar can be judged interchangeable with the reference product if the biosimilar manufacturer can show that the biosimilar produces the "same clinical result" as the reference product in "any given patient" and can be switched with the reference product with no additional risks in terms of safety or diminished efficacy.⁷ Meeting this higher threshold requires submission of additional data, including results from trials in which patients are switched from the reference biologic to the biosimilar. In most states, obtaining this status would allow pharmacists to substitute a biosimilar for the reference biologic without intervention from the prescribing clinician.^{4,5,7}

As several blockbuster biologics have come off patent over the past few years and more are scheduled to do so in the early 2020s, biosimilars are poised to play a crucial role in curbing health care costs. According to some estimates, biosimilars could reduce health care spending by \$54 billion between 2017 and 2026.^{3,8,9}

Market Landscape

As of February 2019, the FDA had approved 17 biosimilars relating to 9 originator biologics (see Table).¹⁰ These numbers might seem to reflect positively on the BPCIA. However, the US biosimilar market has failed to develop to date in 2 important ways. First, not all FDA-approved biosimilars have been marketed. Only 7 of the 17 biosimilars, covering 4 originator biologics, were commercially available to US patients; 9 biosimilars had yet to be commercialized (and the other one is unlikely to launch for business reasons¹¹) (see Table). Second, among biosimilars that have entered the market, price reductions and market penetration have been limited. For example, filgrastim-sndz, the first biosimilar to be approved under the BPCIA, entered the market in September 2015 at only a 15% discount off the originator's list price.¹² By the end of 2016, 5 quarters after its launch, filgrastim-sndz had acquired just 15% to 20% of the US filgrastim market.¹² Similarly, infliximab-dyyb, a biosimilar of infliximab, launched in November 2016 at a 15% discounted price relative to a brand-name biologic,¹³ and it has thus far acquired less than 5% of the US infliximab market.¹⁴ Given their low utilization, biosimilars have not yet achieved policymakers' intended goal of increasing competition and reducing prices.

Table. List of Originator and Follow-on Biologic Drugs Available in the United States as of February 18, 2019

Originator Name	Biosimilar Name	Month/Year Biosimilar Approved ¹⁵	Biosimilar on Market?	Litigation Status
Adalimumab	Adalimumab-atto	Sept 2016	No	Settlement; DE ¹⁶
	Adalimumab-adbm	Aug 2017	No	Ongoing ¹⁷
	Adalimumab-adaz	Oct 2018	No	Settlement; DE ¹⁶
Bevacizumab	Bevacizumab-awwb	Sept 2017	No	Ongoing ¹⁸
Epoetin alfa	Epoetin alfa-epbx	May 2018	Yes, Nov 2018 ¹⁹	
Etanercept	Etanercept-szsz	Aug 2016	No	Ongoing ²⁰
Filgrastim	Filgrastim-sndz	Mar 2015	Yes, Sept 2015 ²¹	
	Filgrastim-aafi	July 2018	Yes, Oct 2018 ²²	
Infliximab	Infliximab-dyyb	Apr 2016	Yes, Nov 2016 ²³	
	Infliximab-abda	Apr 2017	Yes, July 2017 ²⁴	
	Infliximab-qbtx	Dec 2017	No ^a	
Rituximab	Pegfilgrastim-jmdb	Jun 2018	Yes, July 2018 ²⁵	
	Pegfilgrastim-cbqv	Nov 2018	Yes, Jan 2019 ²⁶	
Rituximab	Rituximab-abbs	Nov 2018	No	Settlement; DE ²⁷
Trastuzumab	Trastuzumab-dkst	Dec 2017	No	Settlement; DE ²⁸
	Trastuzumab-pkrb	Dec 2018	No	Settlement; DE ²⁹
	Trastuzumab-dttb	Jan 2019	No	Ongoing ³⁰
Abbreviation: DE, delayed entry ^a Pfizer announced that it will not market infliximab-qbtx given its existing commercialization of infliximab-dyyb. ¹¹				

Which factors account for the lack of commercialization and low uptake of recently approved biosimilars? Manufacturers of the originator biologic products have employed several tactics to delay market entry of already approved biosimilars and impede patient utilization even after a biosimilar successfully launches.

Delaying Market Entry

The primary reasons for delayed market entry include ongoing patent litigation or agreements to defer entry as a result of settling a patent dispute.³¹ For example, Sandoz and Mylan/Biocon reached global settlements with AbbVie and Genentech, respectively, regarding claims that the biosimilars adalimumab-adaz and trastuzumab-dkst infringed

on patents protecting the originator biologics adalimumab and trastuzumab.^{28,32} Arguably, the most notable case of patent litigation leading to the delayed entry of biosimilars involves adalimumab, the top-selling drug in the world. In 2017, adalimumab had \$18.4 billion in global sales, more than double the second best-selling drug, lenalidomide.³³ AbbVie, adalimumab's manufacturer, procured over 100 patents on the product. Although AbbVie's active ingredient patent on adalimumab expired in 2016, it was granted a series of patents protecting everything from the manufacturing process to new formulations of the drug.¹⁶ One 2018 report found that 89% of these patent applications were filed after adalimumab was on the market, and 49% were filed after the first patent expired in 2014.³⁴ This strategy of creating a wall of patents to protect assets^{34,35} is known as developing a "patent thicket."¹⁶

AbbVie sued the manufacturers of adalimumab biosimilars, including Amgen, Boehringer Ingelheim, Mylan, Pfizer, Samsung Bioepis, and Sandoz, for patent infringement, with settlements having been reached in all but one case.¹⁶ These settlements entail a licensing deal in which the biosimilar manufacturers delay entry and pay AbbVie a royalty after they do reach the market.³⁶ As a consequence of these settlements, the first biosimilars for adalimumab are anticipated to enter the US market in January 2023.^{36,37} Annual sales of adalimumab over the remaining years are anticipated to be over \$10 billion, which will add to the cost burdens currently facing payers and patients in the United States.^{38,39,40}

Deterring Biosimilar Prescribing

Utilization of the few biosimilars that have entered the US market, meanwhile, has been suboptimal. One strategy originator manufacturers have employed to limit biosimilar uptake has been to negotiate formulary exclusivity with payers. In a 2017 lawsuit, for example, a biosimilar infliximab manufacturer alleged that the originator manufacturer entered into contracts with commercial payers to exclude biosimilars from drug formularies or include "fail first" provisions, which would require a patient to have failed on the original product before a biosimilar could be reimbursed.⁴¹

Rebate schemes have featured prominently in this practice. The infliximab lawsuit charged that the originator manufacturer told insurers that if they did not grant exclusive use of its product, the manufacturer would withhold rebates on other products.^{41,42} At least 70% of commercially insured patients in the United States are affected by these exclusionary contracts.⁴¹ One study found that among 2547 Medicare Part D plans, only 10% covered the biosimilar infliximab compared to 96% that covered the originator.⁴³

With limited biosimilar availability in the United States, there remains substantial skepticism among prescribers and users relating to the efficacy and safety of biosimilars. A 2016 national survey of US physicians in specialties that have high utilization of biologics found that 55% did not believe that biosimilars were safe and appropriate for

use in patients.⁴⁴ Similar studies have found that patients have low levels of awareness of biosimilars as well as concerns about inadequate efficacy and elevated safety risks of biosimilars that are not consistent with reassuring evidence about their clinical usefulness.⁴⁵ This skepticism has allegedly been promoted by some originator manufacturers. In August 2018, a citizen's petition to the FDA charged that certain biologic manufacturers "mischaracterize important elements of the biosimilar criteria and create doubt and confusion about the safety and efficacy of biosimilars,"^{46,47} citing one Genentech webpage that explains that the "FDA requires a biosimilar to be highly similar, but not identical to the [reference product]," without stating that approved biosimilars have no clinically meaningful differences from the reference product.⁴⁷ The petition also cited patient brochures emphasizing that the biosimilar infliximab was "not approved as interchangeable with" the originator version, which could mislead patients into thinking that biosimilars were unsafe.⁴⁷

Proposed Solutions and Ethical Concerns

Many solutions have been proposed to address the issue of limited utilization of biosimilars.⁵ For example, legislation could be passed to increase the transparency in reporting of biologic patents, which would allow biosimilar manufacturers to more readily challenge their validity. Additionally, regulatory agencies could scrutinize the anticompetitive practices of exclusionary contracts and enact stronger regulations against such practices. Lastly, the FDA could increase its efforts to educate physicians and the public about the bioequivalence of biosimilars and remove unnecessary naming policies that cause confusion among users, including the 4-letter suffixes given exclusively to biosimilars for the sole purpose of distinguishing them from their originators. Addressing these issues will inevitably result in increased biosimilar use. However, are there ethical concerns that arise with expanding the use of biosimilars?

Some have argued that the BPCIA pathway does not sufficiently guarantee the effectiveness or safety of biosimilars, which is at the root of skepticism among patients and physicians.^{44,45} While it is possible that minor structural differences among biosimilars could lead to variable effectiveness and safety, studies to date have found no meaningful differences between a biosimilar and its respective originator biologic with respect to safety and efficacy.⁴⁸⁻⁵⁰ Still, [postmarketing studies](#) of biosimilars will continue to be necessary to evaluate these concerns.

Perhaps the most important question facing policymakers is whether greater use of biosimilars will improve public health. The high cost of biologics remains a significant barrier to patient access and adherence.⁵¹ Although biosimilars will likely remain higher priced than small-molecule generics, price reductions will continue to manifest as more competition is introduced into the market.^{52,53,54} These lower prices will reduce overall health care costs and could improve patients' medication adherence, resulting in better health outcomes.

Although biosimilars have yet to yield the significant cost savings that they were touted to bring, pursuing greater biosimilar competition is a worthwhile goal.³ However, if a low-cost biosimilar market does not result from policies designed to eliminate barriers to entry and utilization, an ethical approach might be to mandate the reduction in the prices of originator biologic drugs after a certain time period on the market.⁵⁵ Such a policy would achieve the goal of providing affordable and accessible therapeutics to patients, but there is likely not political appetite to implement it. Thus, encouraging increased competition in the biologics market with biosimilars remains the most promising mechanism to increase access to much-needed drugs.

The Biosimilars Action Plan

In July 2018, the FDA published its Biosimilars Action Plan, acknowledging the [lack of competition](#) in the biologics space.⁵⁶ Recognizing the numerous barriers to the development and utilization of biosimilars, the FDA outlined 4 key goals in tackling this issue, including streamlining the approval process, improving regulatory clarity, increasing educational efforts to improve understanding among stakeholders, and collaborating with the Federal Trade Commission to address anticompetitive behaviors.⁵³ Despite barriers to their commercialization and uptake, biosimilars remain a powerful tool with potential to lower health care costs and improve patients' access to valuable therapeutics.

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MEDICINE AND SOCIETY

Does Incorporating Cost-Effectiveness Analysis Into Prescribing Decisions Promote Drug Access Equity?

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Abstract

Using cost-effectiveness analysis (CEA) to inform prescribing can promote equitable drug access from a utilitarian perspective. Some theorists of equity, such as Rawls or Powers and Faden, however, would not consider CEA as promoting equity, as they endorse nonutilitarian theories of equity. Novel advances in CEA methodology seek to integrate broader equity concerns but may raise transparency concerns. We argue that incorporating CEA into qualitative multi-criteria decision analysis to inform prescribing decisions could promote equity more effectively and transparently than using CEA alone. Such applications should be implemented, along with recommendations, at the health system level rather than be carried out by individual clinicians alone.

Cost-Effectiveness and Health Equity

Rising prescription drug costs contribute to drug inaccessibility.¹ When clinicians prescribe medications that are not cost effective, insurers subsidize these medications to the detriment of making cost-effective medications more affordable and therefore more accessible. Traditional cost-effectiveness analysis (CEA) promotes economic efficiency by prioritizing health care interventions that maximize health gains across a population within a given budget. Specifically, when a physician selects among several medications to treat a certain condition, using CEA might favor medication that is both more effective and less expensive than the alternatives or medication that delivers the greatest health gain per dollar spent. Incorporating CEA into [prescribing guidelines](#) and decisions has potential to shift insurance subsidies toward more efficient drugs, thus increasing their accessibility to patients.

Yet some ethicists, policymakers, and clinicians worry that the use of CEA fails to promote health equity.^{2,3,4} Equity refers to the fair distribution of morally relevant goods among groups; that is, under a fair distribution, differences among groups are ethically permissible only if the differences are justifiable as not unfair.⁵ Health is one morally relevant good. In the context of CEA, we take health equity to refer to fair distribution of health outcomes or gains. We argue that prescribing guidelines can and ought to incorporate CEA as part of a larger endeavor to promote both health equity and equity

more broadly construed. However, CEA alone, as traditionally applied, is not sufficient to promote equity.

Cost-Effectiveness Analysis and Theories of Equity

Utilitarianism. Traditional CEA is based on a *utilitarian* theory of equity or fair distribution. When applied to health gains, this theory has 2 key parts. First, traditional CEA is designed to inform identification of health services that produce the greatest health gains per dollar spent.⁶ CEA is thus based on a *consequentialist maximization* theory of fair distribution, or the view that we ought to maximize good outcomes. Second, many applications of CEA are cost-utility analyses (CUA) that characterize health gains for a target patient population in terms of health-related utility typically measured in **quality-adjusted life years** (QALYs). (One QALY is equivalent to one year of life lived in perfect health, capturing both morbidity and mortality.) CEA as CUA rests on a type of *welfarist* view in which well-being should morally be the focus of distribution; a welfare maximization approach is known as utilitarianism.⁷ On utilitarian theory, a fair distribution is straightforwardly one in which welfare is maximized; the relative distribution of welfare within a population is unimportant. Thus, for a utilitarian, the application of CEA is equity promoting with respect to health gains.

Other theories of equity. Aside from utilitarianism, other theories of equity suggest that incorporating CEA alone would not be equity promoting with respect to health gains. John Rawls rejected utilitarianism and proposed what's known as a "maximin" principle, whereby inequalities in wealth and income are fair as long as those who are the least well off on this distribution are better off than they would be on any other possible distribution.⁸ This approach to equity is *prioritarian* and differs from utilitarianism because a distribution whereby overall good is maximized would likely be inconsistent with the maximin principle. Additionally, for Rawls, distribution of *primary goods*—income and wealth as well as certain rights and respect—as opposed to welfare is what matters morally.⁸ Later, Norman Daniels extended Rawls' account to include the fair distribution of health and health care.^{9,10} Alternatively, Madison Powers and Ruth Faden advocate a theory that can be roughly described as *sufficientarian* about *capabilities*,⁷ which builds on the work of Amartya Sen.^{11,12} On this view, all people should enjoy a sufficient level of some central capabilities, such as health, self-determination, and the ability to form important social relationships. Unlike Rawls' approach, on this view, the least well off are not strictly prioritized; rather, all should enjoy a minimally acceptable level of well-being in terms of these capabilities.

In light of these varying justice theories, an important question is whether CEA methodology can be adapted to further the goal of equity, both with respect to health gains and more generally. Cookson et al summarize some novel approaches for including equity considerations in CEA analyses, such as distributional CEA (DCEA) and extended CEA (ECEA).⁴ DCEA can compare the distribution of health effects and health opportunity

costs of different interventions by subgroup. DCEA has been used to understand how targeted versus universal health reminders for improving cancer screening uptake affect the distribution of health gains analyzed by sex, ethnicity, and social deprivation.¹³ ECEA can assess the distribution of both health effects and protection against illness-related impoverishment. For example, ECEA has been used to compare the health gains and financial risk protection by income group of a potential cigarette excise tax in China.¹⁴ Both DCEA and ECEA enable decision makers to apply nonmaximization theories of equity, like prioritarianism, by permitting comparison of costs and benefits to a whole population with costs and benefits to subgroups of special concern. Furthermore, ECEA adopts in part a Rawlsian primary goods approach to equity by measuring costs and benefits in terms of income or wealth and not simply health. There have also been efforts to develop nonwelfarist measures of effectiveness for use in CEA. For instance, a capability measure known as ICECAP assesses the impact of health care on capabilities such as autonomy and attachment rather than simply on QALYs.¹⁵

While these approaches suggest it is possible for CEA to promote equity given value pluralism about what constitutes a fair distribution, they raise an additional ethical concern. A primary worry is that methods like these, as Faden and Sirine Shebaya note, “obscure controversial moral considerations from public view and deliberation” and are thus antidemocratic approaches that could harm institutional legitimacy.¹⁶ Because CEA is a complex methodology that requires expertise to understand and apply, addressing equity concerns in CEA—and doing so in a highly technical manner—could mean that many people are unable to identify and challenge the values informing CEA analyses with which they disagree.

To be sure, this objection can be levelled at traditional CEA itself, an approach based on several value assumptions with implications for equity. For example, health gains are typically considered equally valuable regardless of age or illness severity; different discounting rates for long-term costs or effectiveness assign different value to current versus future lives and assign different value to prevention versus treatment; and there is in-built impartiality regarding whether and when large benefits to a small population should outweigh small benefits to a large population, an issue catapulted into public consciousness when Oregon proposed covering tooth capping but not appendectomies under Medicaid.¹⁷

How to modify CEA models to align with different views on equity is a complex matter about which reasonable people will likely disagree. Transparency about values at play in CEA—achieved by publishing and disseminating either outcomes of decision-making processes that use CEA or the full rationale behind those decisions—in a way that is both accessible and comprehensible to members of the public¹⁸ is necessary for informed and accessible debate about which values should inform our health care practices and policies.

Alternative Approaches

Given the potential for a lack of transparency about the values at play in CEA, another way to promote equity would be to retain traditional CEA for its value in promoting efficiency—and equity from a utilitarian perspective—but consider it *alongside* analyses that capture other equity theories' core values. In multicriteria decision analysis (MCDA), for example, decision makers evaluate a set of potential interventions across several criteria to determine which interventions should be **prioritized**. That is, rather than building additional considerations into a single analysis as in DCEA and ECEA, MCDA enables cost effectiveness to be weighed alongside equity-relevant considerations intended to target certain subpopulations defined, for example, by disease severity, age, or socioeconomic status.¹⁹ Importantly, *qualitative* MCDA eschews the mathematical aggregation of scores across multiple criteria and instead relies on decision makers' deliberation about the relative value of these criteria in order to prioritize subgroups or interventions.²⁰ In this way, qualitative MCDA can better promote transparency than approaches that quantify equity considerations and integrate them into a single analysis, as in traditional CEA, DCEA, or ECEA.

Justice-enhanced CEA is another approach being developed to assess equity within the context of drug-resistant tuberculosis and other infectious diseases. This method, influenced by the work of Powers and Faden,¹¹ aims to assess health care interventions' impact on core aspects of social justice, such as agency, association with others, and self-respect or social respect. These social justice impacts can then be considered alongside outputs of traditional CEA in order to improve equity.^{21,22} For instance, novel medications for drug-resistant tuberculosis allow treatment regimens to be shorter, thus reducing the time during which patients endure social stigma due to this specific illness. Although these novel drugs might be less cost-effective than existing regimens, they might better protect patients from social exclusion. In theory, the influence of different health care interventions on agency, association, and self-respect could also be considered in qualitative MCDA approaches to equity.

Prescribing Policies

Unlike some other developed countries, the United States does not have organizations that provide guidelines for coverage and prescribing based on CEA. The Patient-Centered Outcomes Research Institute (PCORI), for example, created by a clause in the Patient Protection and Affordable Care Act, is not allowed to use CEA to inform recommendations.²³ Considering this limitation at the federal level, our recommendation is instead for health systems—hospitals, physician groups, or health centers—to issue prescribing guidelines informed by traditional CEA *and* qualitative MCDA that includes explicit and diverse equity considerations like those discussed above. For example, health care organizations' boards or panels of clinicians and ethicists could deliberate regularly using MCDA to (1) assess interventions' cost-effectiveness and impact on

various dimensions of equity and (2) issue recommendations to clinicians about new interventions or those already in use.

We believe that this approach is superior to a system in which individual clinicians alone incorporate CEA in their prescribing decisions. Involving clinicians directly in cost containment measures has been criticized,^{24,25} and, in general, bedside rationing raises a number of complex ethical issues^{26,27} and may be too burdensome for individual clinicians to implement alone. As we have argued, a qualitative MCDA approach can better promote transparency about the reasons for a decision. Decision-making processes that incorporate MCDA should also include other elements of a fair process, such as opportunities for clinicians and patients to appeal decisions,^{28,29} given that reasonable people are likely to disagree about what promoting equity demands. Whether CEA promotes equity depends on the theories of equity one supports and on the values incorporated in different CEA models. Traditional CEA can help expand access to cost-effective interventions, and, when used alongside explicit equity considerations in a deliberative manner, can help more appropriately balance efficiency and equity impacts.

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HISTORY OF MEDICINE

How Do Drugs Get Named?

Gail B. Karet, PhD

Abstract

Since the 1960s, the United States Adopted Names Program has been assigning generic (nonproprietary) names to all active drug ingredients sold in the United States. Pharmaceutical names are assigned according to a scheme in which specific syllables in the drug name (called stems) convey information about the chemical structure, action, or indication of the drug. The name also includes a prefix that is distinct from other drug names and that is euphonious, memorable, and acceptable to the sponsoring pharmaceutical firm. Drug names are the product of complex, multiparty negotiations in which the needs and desires of various stakeholders (patients, pharmaceutical firms, physicians, pharmacists, other health care professionals, and US and international regulators) must be balanced.

Overview of Generic Naming

The assignment of generic names to pharmaceuticals in development is an important prerequisite to marketing a drug. The United States Adopted Names (USAN) Program, which assigns generic (nonproprietary) names to all active drug ingredients in the United States, is the result of a long-time partnership between the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA). These 3 organizations are the sponsoring partners and receive support from the US Food and Drug Administration (FDA).

In the United States, the FDA recognizes the USAN as the legal name for the active drug ingredient, and the USAN appears in the titles of monographs published by the USP that define the standards, properties, and characteristics of marketed drugs. With few exceptions (eg, prophylactic vaccines and mixtures not named by the USAN Council), a drug cannot be marketed in the United States without a USAN. Consequently, the USAN assignment is a necessary step in drug development before a drug can be brought to the US market, and assignment of a USAN is required for a new drug before patients can have access to it.

Outside the United States, the World Health Organization (WHO) publishes recommended International Nonproprietary Names (INN) for active drug ingredients, but

the INN is not a substitute for a USAN. The USAN and the INN programs work together to ensure that generic names are the same inside and outside the United States. Consequently, the generic names inside and outside the United States differ only rarely, and these differences can potentially be very important. An example of a drug with 2 names is the substance known as acetaminophen inside the United States and as paracetamol internationally,^{1,2} although these 2 names predate the inception of the USAN Program.

Firms usually begin the process of obtaining a nonproprietary name by filing a submission with the USAN Program or the WHO when a drug is in phase I or phase II clinical trials. Most prefer to complete generic name assignments by the time they are ready to publish papers about the drug so that they can use the name instead of a manufacturer code in publications. The USAN must be assigned before conducting premarketing labeling negotiations with the FDA.

The USAN Council is committed to patient safety, facilitating communication among health care professionals and patients, and access to prescription medications. The USAN Council is, therefore, aware of the importance of coining names that will not be confused with other drug names, compromise patient safety, or mislead health care professionals and patients about the action or use of a new drug substance. The USAN Council is also mindful of concerns that high drug costs can limit patients' access to them and, accordingly, must weigh this possibility against the possibility that pharmaceutical companies may choose not to develop drugs that they believe will not be profitable when they make their nomenclature decisions. Because the USAN name includes information about a drug's structure, action, or planned use, the name can potentially affect how a drug is perceived by physicians, pharmacists, pharmacy benefits managers, or the investment community. These perceptions can affect drug pricing and which drugs companies choose to advance in clinical trials.

USAN Program History

The USAN Program originated with the AMA's Council on Pharmacy and Chemistry, which was created in 1905 to evaluate drugs and to try to eliminate [quackery](#) in medications.³ In 1938, the Food, Drug, and Cosmetic Act established federal regulatory authority over drugs, including requiring proof of safety,⁴ but the AMA's Council on Pharmacy and Chemistry (renamed the Council on Drugs in 1957⁵) continued to evaluate drugs, and the AMA had laboratory facilities for this purpose. From 1907 through 1964, the AMA published an annual volume called *New and Nonofficial Remedies (NNR)*, renamed *New and Nonofficial Drugs (NND)* in 1958.^{3,5} The AMA also published *Epitome of the United States Pharmacopeia and National Formulary* annually between 1907 and 1955.³ Both AMA publications listed drugs by name along with information about their properties, use, or efficacy. In 1962, the Food, Drug, and Cosmetic Act was amended to give the FDA the authority to approve—or not approve—a drug based on evidence of efficacy as well

as safety in the wake of the thalidomide tragedy.⁶ After passage of this law, the AMA continued to publish information on drugs.

Until 1963, the AMA's Council on Drugs did not adopt the position that drugs should be labeled so that patients would know what they were taking, and when it did adopt this position, it expressed the belief that patients should sometimes not be informed what was in their medications.⁷ Several circumstances under which it was better for patients not to know the identity of their medicines were described: when patients were taking opioids or barbituates, when they might try to "out-guess the doctor" and make decisions themselves, or if patients regarded medications as "magical potions." The Council favored labeling as a general practice, but recommended that prescription pads include boxes for "yes" or "no" to indicate whether the drug should be labeled, with the default being labeling.

Meanwhile, the AMA's future partners in USAN were conducting their own nomenclature activities. The American Pharmaceutical Association, later renamed APhA, began publishing the *National Formulary* in 1888.⁸ The USP, which incorporated in 1900, was tasked with publishing reference standards for strength, quality, and purity in the Pure Food and Drug Act of 1906.^{9,10} The USP published compendia of monographs describing these standards, with the drug name as the monograph title.

On July 22, 1960, the AMA, the USP, and industry representatives met at the USP Conference on Nonproprietary Names for Drugs to discuss not only nonproprietary names for drugs but also to review a proposal to transfer nomenclature to a single entity. Concerns were raised that the existing system did not require selection of a nonproprietary name for each drug, that there was no central list of names, and that there was no legal requirement that all firms use the same name for a substance.

In a proposal to the AMA dated November 7, 1960, the USP called the program that later became USAN a "cooperative program for the selection of non-proprietary names of drugs." The draft of the proposal stated, "The American Medical Association will maintain and expand, as necessary, its present facilities for receiving proposals of nonproprietary names from all sources, will process these proposals and initiate and conduct such negotiations expeditiously as may be appropriate to settle upon a tentative name for all new drug entities." The USP committed to adopting the selected names as USP monograph titles and to publishing lists of the names.

The founders sought to achieve industry cooperation and preferred not to involve the federal government in nomenclature. A July 15 memorandum sent by the USP's Lloyd Miller to participants shortly before the USP Conference on Non-Proprietary Names for Drugs stated, "The industry seems to have no special preference as to what agency acts as a clearing-house. There is a desire, however, to keep the name selection program

separate from processing the FDA new drug applications. The FDA has not been disposed heretofore to concern itself very much with nonproprietary names.”

Following these discussions, the AMA-USP Nomenclature Program was established in June 1961.

In 1963, the APhA joined the AMA and the USP in sponsoring the committee’s nomenclature efforts. The partners agreed the council would include 3 representatives from each of the sponsoring organizations and a member at large. The committee was renamed the USAN Council, and the selected names were to be known as USAN. The USP agreed to adopt USAN as USP monograph titles, and the APhA, through its Committee on National Formulary, agreed to adopt USAN as *National Formulary* titles. In 1967, the agreement was further amended, and a representative from the FDA was added to the council. It was agreed that AMA staff would maintain all contacts in connection with the process of selecting and negotiating names. The USAN Council would—and still does—function independently of the FDA and is not an FDA advisory body.

What USAN Names

Over 10 000 drugs have received nonproprietary names since the WHO, AMA, USP, and APhA began assigning names to drugs,¹¹ and they are listed in online databases such as the *USP Dictionary of USAN and International Drug Names*.¹ In 2018, the USAN program named 198 substances. The number of USAN adoptions fluctuates from year to year but has grown steadily over the past 20 years.

By reviewing the chemical information published on the statements of adoption for each compound, it is possible to determine what types of substances were named (Table 1). Of all the drugs named in 2018, 112 (57%) were chemical substances (organic molecules) or their salts or esters intended as drugs for human use. The USAN Program named 76 substances (38%) that were biological in nature, including gene therapies, cell therapies, oligonucleotides, monoclonal antibodies and antibody drug conjugates, and other proteins or peptides. **Biologic drugs** tend to be expensive, and the path for approval of generic versions of these products is different than for small molecules.¹²

Table 1. Types of Substances Named by United States Adopted Names Program, 2018

Type of Substance	Number Named
Antibody-drug conjugates	1
Cell therapies	6
Chemical substances, organic molecules	83
Salts or Esters of chemical substances	29
Gene therapies	9
Inorganic salts or solid-state compounds	1
Monoclonal antibodies	41
Oligonucleotides	10
Peptides	3
Polymers	8
Proteins (not monoclonal antibodies)	6
Other types of substances	1
Total	198

The USAN Program publishes the planned therapeutic indication that the firm discloses when it applies for a name on the statement of adoption (see Table 2). In 2018, 71 substances (36%) named were intended for use as antineoplastics (ie, oncology drugs that attack tumors). Other popular indications for new substances named include neurologic conditions such as Parkinson’s disease (22 substances or 11%), [infectious diseases](#) (18 substances, or 9%), and rare, inherited disorders such as Crigler-Najjar syndrome or Fabry disease (24 substances, or 12%). Relatively few drugs (or none) were named for common conditions affecting large numbers of patients, such as diabetes, depression, or high blood pressure.

Table 2. Planned Therapeutic Indications of Substances Named by the United States Adopted Names Program, 2018

Indication	Number Named
Anti-infectives	17
Antineoplastic compounds, oncology	72
Arthritis	1
Contact lens polymers	6
Analgesic	3
Cardiovascular indications other than high cholesterol	5
Cholesterol (high cholesterol)	1
Dermatology	3
Diabetes and related metabolic disorders	0
Diagnostic agent	1
Gastroenterology	1
Genetic disorders (eg, lysosomal storage disorders)	23
Gynecologic	2
Hepatology	2
Immunomodulatory indications (eg, psoriasis)	10
Muscular dystrophy and muscular conditions	5
Neurologic indications (eg, Parkinson's, Alzheimer's)	22
Ophthalmology indications	3
Psychiatric indications (eg, depression, schizophrenia)	2
Respiratory indications (eg, asthma, cystic fibrosis, COPD)	6
Urology	2
Veterinary pharmaceuticals	3
Other indications	5
Multiple indications	3
Total	198

Developing new drugs for common conditions for which drugs already exist poses challenges. Pharmaceutical companies are for-profit entities that seek to maximize returns and minimize potential risks, and developing new drugs is a high-risk enterprise. Although there has been some debate about the exact cost of developing a drug, the most widely disseminated recent estimate is that it costs about \$2.6 billion to bring a drug to market.¹³ Although failure rates vary according to the therapeutic class, most drugs that enter clinical trials fail.¹⁴ Thus developing new drugs that target existing mechanisms and are differentiated from existing products in a clinically meaningful way can be challenging.¹⁵ Consequently, pharmaceutical companies might find it more financially viable to develop drugs when there is less competition from low-cost therapies.

It is not clear whether firms' focus on oncology and [rare diseases](#) or on expensive biologic drugs—potentially with less emphasis on developing affordable drugs for conditions affecting many people (eg, diabetes, high blood pressure)—restricts access to adequate care. If low-cost prescription drugs already available to treat common chronic conditions are adequate, new treatments, which tend to be more expensive than older drugs, might not be needed.

What Names Mean

In naming drugs, the most important considerations are avoiding drug names that are too similar to existing names—and therefore might compromise patient safety—and making sure the drug name communicates accurate information about the action or use of the substance. Over time, the USAN and INN nomenclature scheme has developed into a system for classifying new pharmaceuticals.

Many of the oldest drugs were named by shortening the systematic chemical name for the compound. However, the AMA-USP Nomenclature Committee quickly realized that a different way of naming drugs was needed and published a list of guiding principles to systematize nomenclature and move away from names derived from the chemical name of a substance.¹⁶ At that time, the AMA-USP Nomenclature Committee recognized 3 difficulties with chemically derived names: (1) the use of chemical syllables led to “complex, unmanageable” names for large classes of chemically related drugs; (2) common, chemically derived syllables (eg, di-, chlor-, meth-) were so overused that names were becoming less distinctive; and (3) some chemical compounds were so complex that the names derived from the proper chemical name were not meaningful to physicians.

Consequently, most USAN now include a stem. A stem consists of syllables—usually at the end of the name—that denote a chemical structure, indication, or action at a specific receptor. For example, in the name imatinib, the -tinib stem refers to the drug's action as a tyrosine kinase (TYK) inhibitor. Occasionally, a substem is used to further classify a

drug. Thus, -citinib refers to drugs inhibiting a specific family of TYK inhibitors, the Janus kinases. There are currently over 600 stems and substems that have been defined for classes of drugs.¹⁷

A 1- or 2-syllable prefix at the beginning of each name differentiates each drug from other members of the same class. The most important concern in choosing a prefix is patient safety—specifically, reducing the risk of medication errors, which are a common and long-standing problem in medical practice.^{18,19} For this reason, the USAN Council avoids prefixes that will create new names that are too similar either to other drugs in the same stem class or to names in other stem classes that might look or sound similar to the new name. This means comparing drug names against lists of names for existing drugs. The USAN Program carefully screens prefixes using searches of databases of existing drug names^{1,11} and Phonetic and Orthographic Computer Analysis (POCA) software.²⁰ The USAN Program, as much as possible, also avoids creating new drug names that begin and end with letters shared with existing generic or trade names for drugs or that have been found to have strong conflicts with other names in the POCA analysis. An analysis of trade-name pairs prone to look alike-sound alike medication errors found that these pairs often had shared strings of 3 or more letters in the prefix and POCA scores that indicated a conflict.²¹

Balancing the Needs of Firms and Patients

As with any complex multiparty negotiation, there can be disagreements. The USAN Council's focus on patient safety, access to new drugs, and communicating necessary information about drugs through the generic name is sometimes in conflict with the desires of pharmaceutical companies to create either a certain message about their drugs through the generic name or a positive image for their substances. While this desire on the part of companies is understandable, the USAN Council prioritizes patient safety and access to affordable drugs.

The class to which a drug is assigned can indirectly affect a company's decisions about whether or not to continue developing it. Sometimes there are financial benefits if a drug is assigned to a specific drug class, and assignment to an undesirable drug class (often one in which there have been safety problems) might adversely affect drug development. Because pharmaceutical firms are in business to generate profits for their investors, they tend to develop more drugs in classes that they believe are commercially viable.

The USAN can also affect how a drug is perceived by payers or pharmacy benefits managers, who may be reluctant to list a "me-too" drug in their formulary but may accept an expensive drug if it is a first-in-class therapy because it is perceived as offering added value that justifies a higher price. For a small biotech firm, a first-in-class drug may be perceived as more valuable by investors or by larger, more established pharmaceutical firms looking to acquire the rights to develop and market new drugs.

Firms might therefore request assignment of a new stem to indicate a drug is first in class. First-in-class drugs can achieve a larger market share, but the second or third member of a class can be a successful product if it improves on the first product in a clinically significant way.^{22,23,24}

The USAN Council must therefore be mindful of how firms' desires for a drug to be named a specific way might affect access to medications and how much those medications cost. Assignment of a new stem is rare, occurring only after the council determines that a drug is truly novel and does not fit into any existing group. Unnecessary assignment of a new stem could lead insurers and patients to pay more for drugs similar to older, less-expensive products, indirectly affecting patients' access to drugs. Similarly, an unfavorable nomenclature decision for the firm, if it contributes to a company's decision to discontinue a developmental drug, might affect patient access.

Conclusions

For decades, assignment of a USAN has been a key step in the development and marketing of a new active pharmaceutical ingredient, because a substance cannot be marketed in the United States without a name. The primary goals of the USAN Council are to facilitate the safe use of medications by assigning names that are unlikely to result in medical errors and to ensure that drug names are reflective of what physicians, pharmacists, and patients need to know about each substance. The USAN can affect how payers, health care professionals, patients, and the investment community perceive a drug—and therefore patients' access to drugs.

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Gail B. Karet, PhD is a senior scientist at the United States Adopted Names (USAN) Program in Chicago, Illinois, and has been supporting the USAN Council in its deliberations on generic name assignment for 15 years. In this role, she facilitates negotiations between pharmaceutical firms, the USAN Council, and the World Health Organization to name drugs undergoing clinical development. She received a PhD in chemistry from Northwestern University.

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ART OF MEDICINE

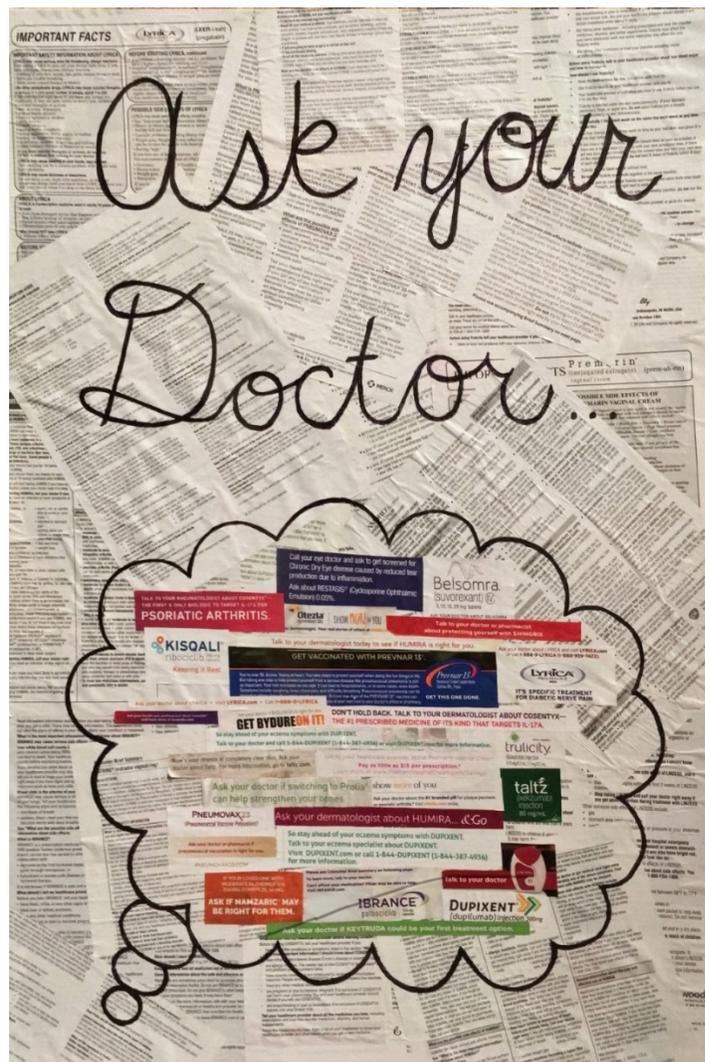
If _____ Is Right for You

Alana Noelle Snyder

Abstract

This mixed media collage, assembled from magazine drug advertisement fragments, explores pharmaceutical companies' influence on the daily lives of American citizens and on patient-physician relationships.

Figure. *If _____ Is Right for You*



Media

Mixed media collage.

This work is a mixed-media exploration of how pharmaceutical companies can influence the daily lives of physicians and members of the public through consumer media. Using a single year's subscription to 2 popular magazines, *If _____ Is Right for You* is assembled from drug ads torn from each magazine. The layering of prescription drug advisory pages mimics the barrage of highly specific technical information that permeates print media. These advertisements target patients, and physicians must respond to those patients' questions, concerns, and enthusiasm about a drug since they have authority to write a prescription.

Logos and slogans centralize a theme to a viewer. Although designed to be aesthetically pleasing, labels and slogans can lead patients to ask for unnecessary or inappropriate medication. The phrase "Ask your doctor if _____ is right for you" facilitates pharmaceutical companies' intrusion on patient-physician relationships and clinical encounters.

Alana Noelle Snyder is a third-year medical student at the University of South Florida Morsani College of Medicine in Tampa. She has been an avid participant in the visual and musical arts since early childhood. Although currently unsure of her future specialization, she wants to continue to bring the joy of art into the practice of medicine.

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ART OF MEDICINE

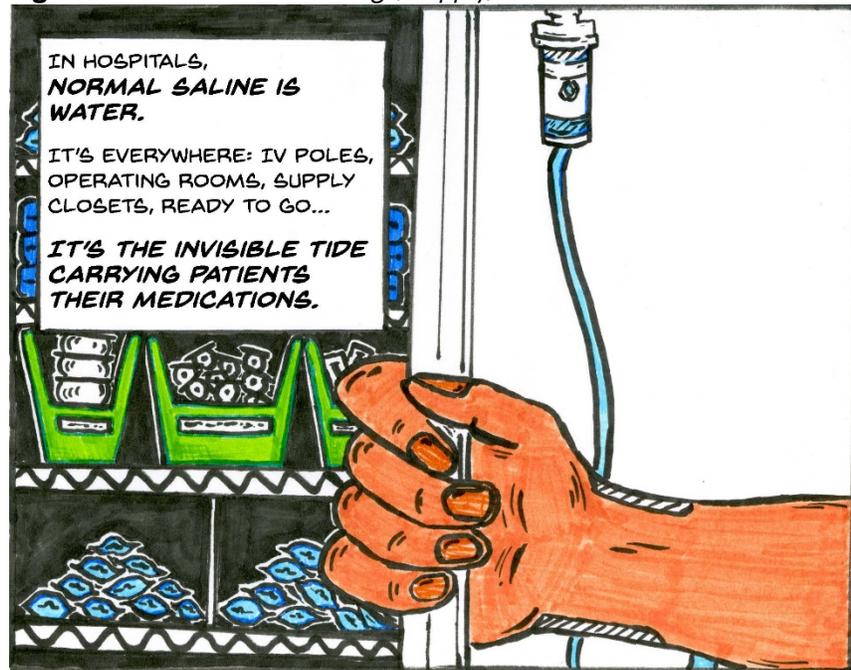
Normal Saline

Hannah Rebecca Abrams

Abstract

In 2017, Hurricane Maria devastated Puerto Rico and prompted a shortage of normal saline in US health care organizations. This graphic narrative considers ethics and justice in the supply, demand, and allocation of intravenous fluids in clinical settings during this time.

Figure. "Normal" Saline: Shortage, Supply, and Solutions



([Click here](#) to view the entire graphic narrative.)

Media

Marker and pencil on printing and tracing paper.

In 2017 and 2018, more than 40 critical medications were in short supply following destruction of drug manufacturing plants in Puerto Rico by Hurricane Maria.¹ In response, government agencies, clinicians, and health care organizations coordinated intravenous fluid allocation to US-based clinical settings. This crisis illuminated the need

for researching saline conservation and triage protocols and for diversifying medication suppliers' manufacturing sites.

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Hannah Rebecca Abrams is a fourth-year medical student at Baylor College of Medicine in Houston. She earned a bachelor's degree in Latin American Studies from Rice University.

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ART OF MEDICINE

Selected Drawings From *Corpus Delicti*

Tracy Meyer

Abstract

Corpus Delicti is a collection of drawings on 30" × 22" paper. Each is inspired by seeds, which hold quiet, hidden potential for transformation and regeneration. Botanicals are familiar but mysterious in their capacity to enact cycles of birth and death. In nature as in medicine, themes of health, illness, reciprocity, and vulnerability are essential features of participation in these cycles. Patients and clinicians in particular negotiate compassion, respect, and dignity in their relationships and clinical encounters. These drawings offer visual exploration of these and other values.

Figure 1. *Yellow Body (State 1)*, by Tracy Meyer with Collaborating Tamarind Institute Printer Sharron Throp



Media

2-color lithograph, Edition 9.

Caption

One night while searching for a certain shade of yellow, I looked up to see the moon emerging from a corpus luteum of clouds. Just as a follicle is induced to open and provides evidence of life at its boundary, so shared decision-making processes emerge in the patient-clinician relationship.

Figure 2. *Yellow Body (State 2)*, by Tracy Meyer with Collaborating Tamarind Institute Printer Sharron Throp



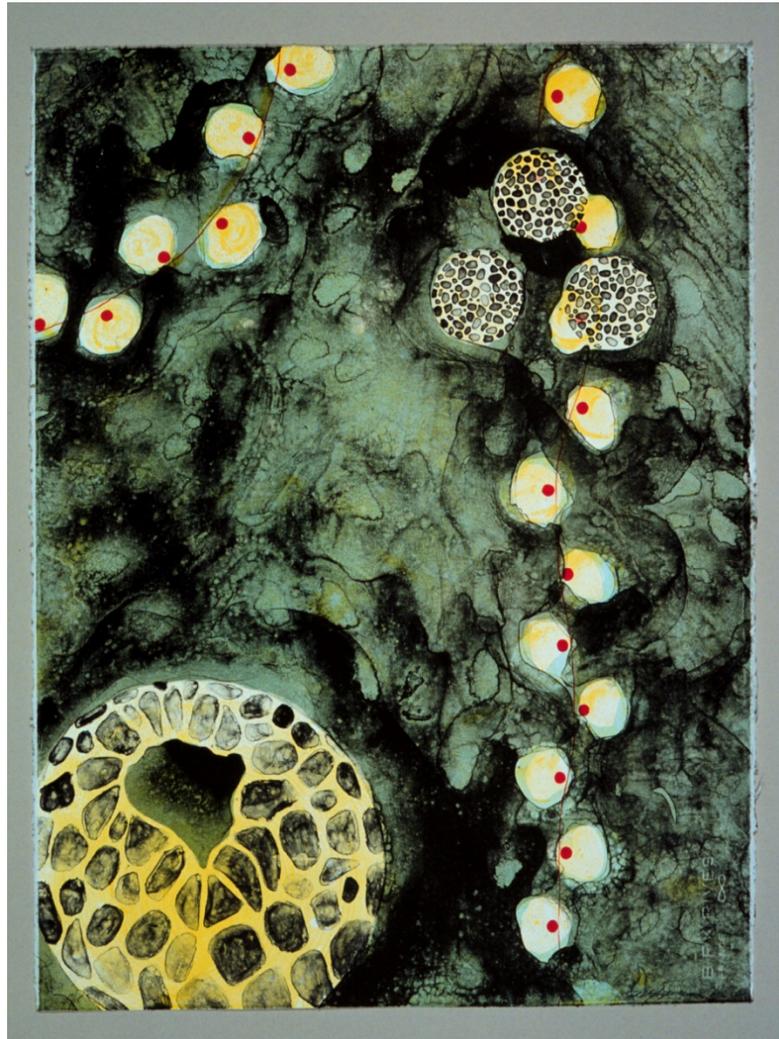
Media

2-color lithograph, Edition 9.

Caption

Two hues of yellow provide ground for release and growth. Just as a seed is a unit of transduction, so trust can be construed as a critical nutrient for therapeutic potential in patient-clinician interactions.

Figure 3. *Remission*, by Tracy Meyer with Collaborating Tamarind Institute Printer Brian Garner



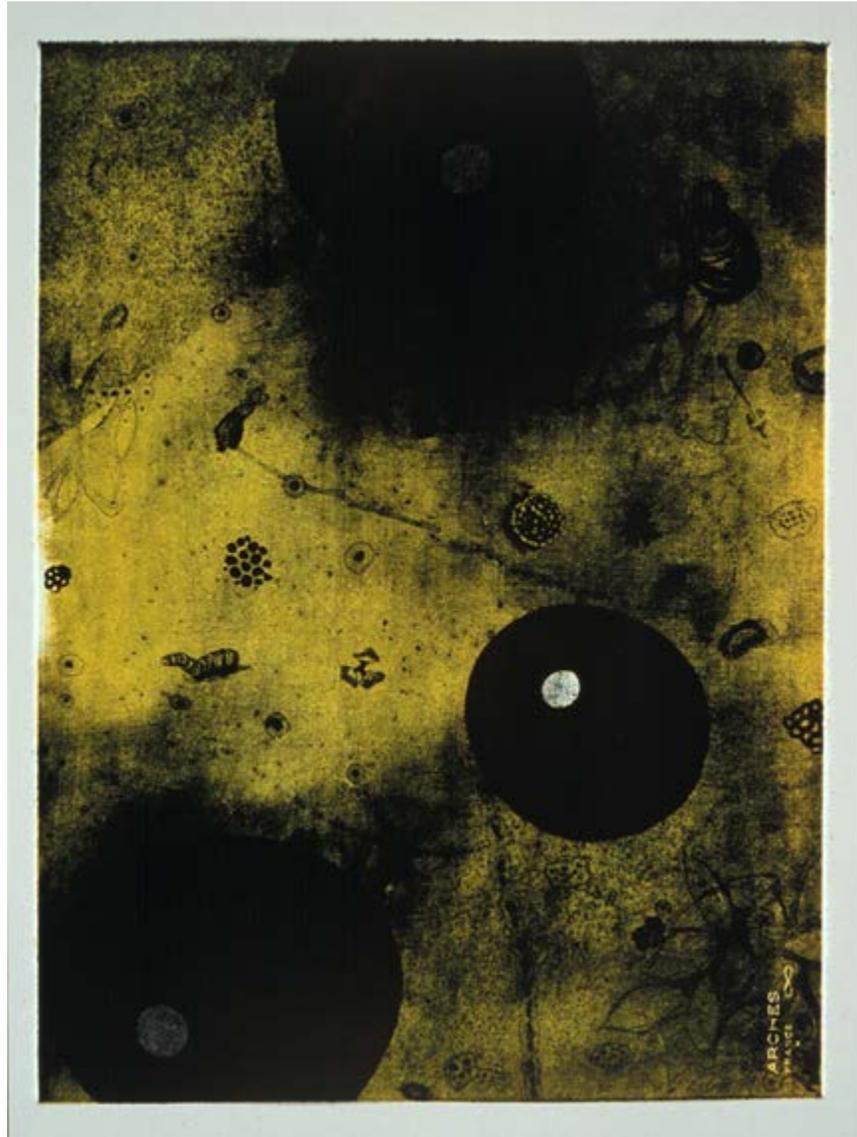
Media

5-color lithograph, Edition 15.

Caption

Draping pods and dividing cells seem to spread darkness apart and enable emergence of brightness, as perhaps occurs when a patient's disease is in remission.

Figure 4. *Dark Lumen*, by Tracy Meyer with Collaborating Tamarind Institute Printer Catherine Chauvan



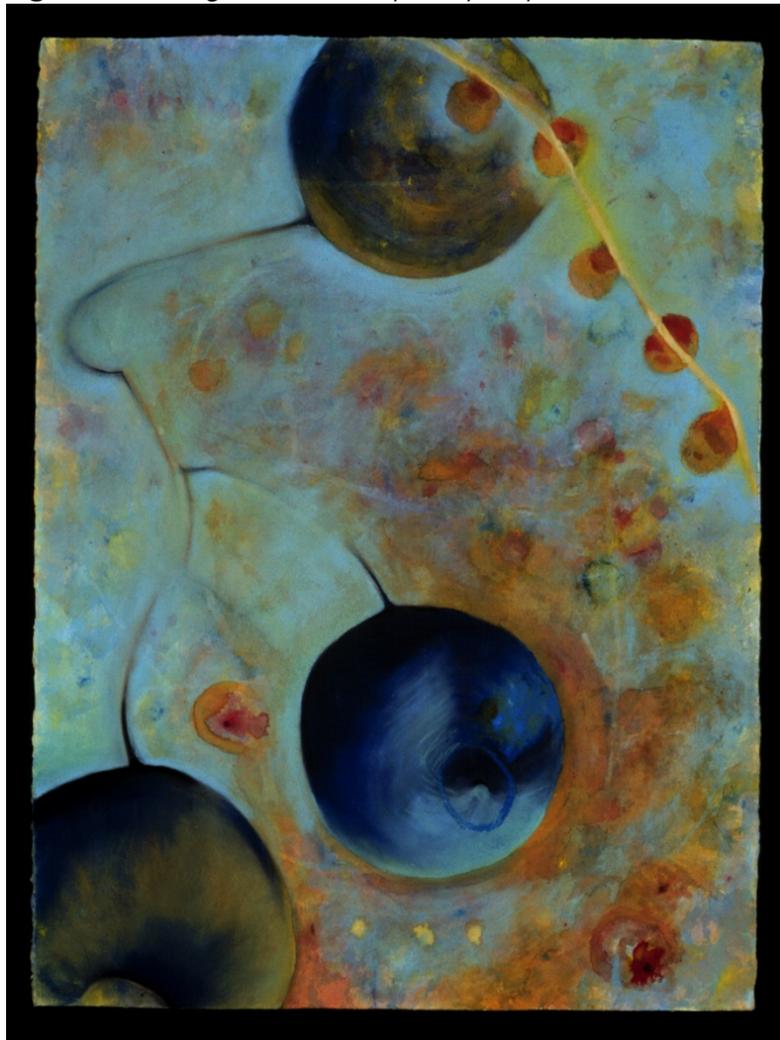
Media

4-color lithograph, Edition 15.

Caption

Organic forms suggest transformation, as one's body can be considered a gateway to, a window on, or a vessel for one's passage through life. Patients' encounters with clinicians can be critical steps along this passage, and clinicians' capacity for compassion and empathy gives shape to patients' experiences and remembrance of those encounters.

Figure 5. *How Night is Divided*, by Tracy Meyer



Media

Pastel, ink, gouache, watercolor, and conté.

Caption

This drawing of cells dividing in a growing seed suggests a growth of space as boundaries are expanded. Boundaries can be construed as preserving a safe enclosure for making sense and meaning of illness or injury, but they are permeable, too, presenting opportunities for us to grapple with uncertainty.

Figure 6. *Misericordia (Soft Angled Skin)*, by Tracy Meyer



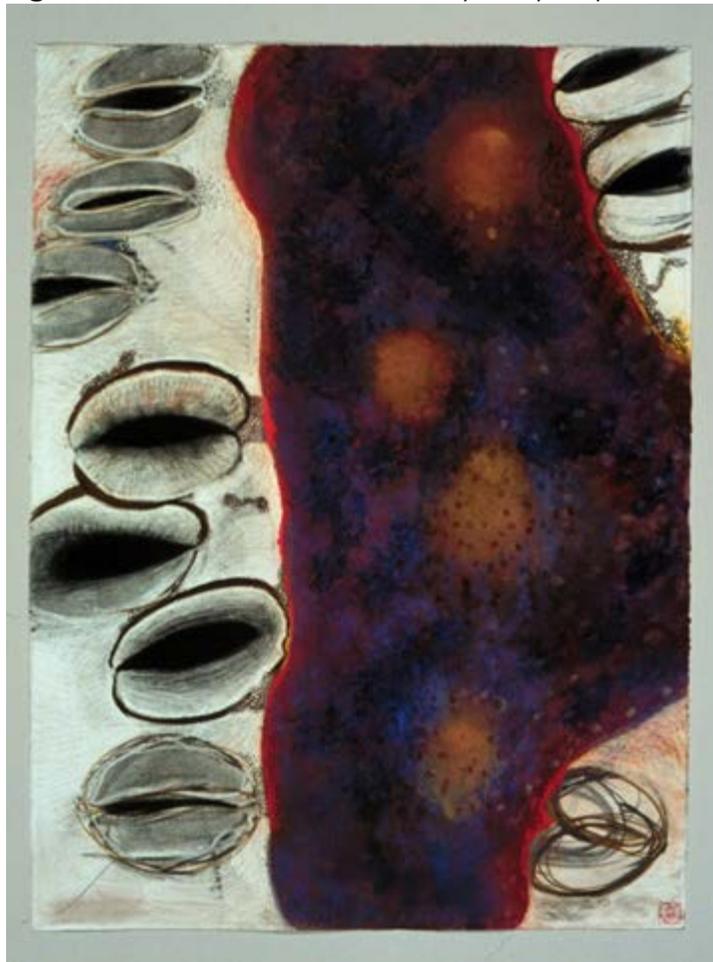
Media

Pastel, charcoal, and conté.

Caption

Just as a clinician's gentle touch can be felt on a patient's skin as an expression of respect and mercy, so exterior skin protects regenerating corpuscles beneath.

Figure 7. *Misericordia (Vital Breaths)*, by Tracy Meyer



Media

Pastel, charcoal, conté, and ink.

Caption

Through a process of covering and erasing, blacks, whites, and grays form the pod figures. The drawing reveals a reservoir of color, of germinative power. This drawing expresses patient-clinician relationships through a visual metaphor of breath: inhalation and exhalation are reciprocal, one relies on the other for purpose and for healing.

Tracy Meyer is an artist, writer, and instructional systems designer. Like her biomorphic artwork, the performance improvement and learning interventions she creates usually have as their subject matter the body, life, death, wellness, illness, medicine, and health care.

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