

DAY ONE PROJECT

An Evidence-based Approach to
Controlling Drug Costs

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Summary

Optimizing the dosing of many expensive drugs can drastically reduce both costs and toxicities. The Federal Government, state governments, employers, and individual patients could collectively save tens of billions of dollars each year by simply optimizing the dosing of the most expensive prescription drugs on the market, particularly in oncology. Optimized dosing can also improve health outcomes. The next administration should, therefore, launch an effort to control the cost of prescription drugs through an evidence-based approach to optimizing drug dosing and improving outcomes. The requisite trials pay for themselves in immediate cost savings.

Challenge and Opportunity

Americans may be polarized about many issues, but a stunning 79% of us agree that the costs of prescription drugs are unreasonable. A majority of Republicans and Democrats alike think that members of Congress—from both parties—are not doing enough to address the issue.¹

Between January 2006 and December 2017, retail prices for 113 chronic-use, brand-name drugs increased by an average of 214%.² These costs are literally killing people. Large numbers of patients regularly abandon life-saving and life-extending treatments simply because they can't afford them. One quarter of all cancer patients, for example, have chosen not to fill a prescription due to cost. Another 20% have chosen to fill only part of a prescription, or to take less than the prescribed amount, for the same reason.³ In other words, hundreds of thousands of Americans are rationing the drugs they need to fight cancer because they have no alternative, a scenario likely worsened by the pandemic.⁴ This is an untenable situation that demands action.

The drug-affordability problem is due in part to the fact that some of the most expensive drugs are prescribed at far higher doses than required to produce an optimal therapeutic effect.⁵ Drug companies normally determine dosing early in clinical trials and rarely take steps to optimize dosing after drugs are approved by the FDA. This is particularly true if the approved dose is higher than is optimal, since optimizing to a lower dose after the drug price is set would reduce

¹ KFF. Poll: Majorities of Democrats, Republicans and Independents Support Actions to Lower Drug Costs, Including Allowing Americans to Buy Drugs from Canada. <https://www.kff.org/health-costs/press-release/poll-majorities-of-democrats-republicans-and-independents-support-actions-to-lower-drug-costs-including-allowing-americans-to-buy-drugs-from-canada/>

² Schondelmeyer, S.W.; Purvis, L. (2018). **Trends in Retail Prices of Brand Name Prescription Drugs Widely Used by Older Americans: 2017 Year-End Update**. AARP Public Policy Institute. <https://www.aarp.org/content/dam/aarp/ppi/2018/09/trends-in-retail-prices-of-brand-name-prescription-drugs-year-end-update.pdf>.

³ American Cancer Society, i2017. **Cancer Facts & Figures 2017**. <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html>

⁴ American Cancer Society, 2020. **Cancer Facts & Figures 2020**. <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html>

⁵ Serritella, 2020. **Interventional Pharmacoeconomics: A Novel Mechanism for Unlocking Value**. <https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1853>

revenues. In short, companies have a perverse incentive to sell as much drugs as possible at the highest price they can and are not typically required by FDA to evaluate lower doses after approval.

This means that there is an enormous opportunity to decrease the costs of disease treatment and improve outcomes through clinical trials to optimize dosing regimens. These types of trials will often result in lower amounts of drugs being given to patients, decreasing drug toxicity and resulting in other beneficial side effects.

Plan of Action

There are several ways to control the cost of prescription drugs. The approach that receives the most attention entails intervening in the market to limit drug prices and the rate at which those prices can be raised. The pharmaceutical and biotechnology industries naturally push back hard against such limits on profit, arguing that they depend on high revenues to reinvest in the development of new products. This argument is credible in theory, but not in practice. Publicly reported profits for pharmaceutical and biotechnology companies often far exceed research and development budgets, indicating that only a small amount of profits are directed towards the discovery and development of new drugs, many of which are “me-too” products, but without apparent benefit of price competition.⁶ Limits on drug prices and price inflation rates should therefore be considered an appropriate and necessary approach to controlling drug costs. But it is by no means the only solution.

There is also a pressing need and opportunity for an evidence-based approach to controlling costs by optimizing dosing and delivery of prescription drugs. For instance, most modern cancer drugs are administered in doses that far exceed the amount needed to produce the desired therapeutic effect.⁷ Drugs like abiraterone (administered for prostate cancer), lapatinib (breast cancer), pazopanib (renal cancer and sarcoma), and nilotinib (chronic myelogenous leukemia) all have profound food effects: that is, they are much better absorbed with food than on an empty stomach. Yet these drugs are all labeled to be taken only while fasting. The result is that far higher doses of these drugs are recommended than are actually necessary, resulting in a cost of treatment for every patient that is far higher than is actually necessary. This mismatch also creates a risk of overdose (which can be fatal) if patients unwittingly take the recommended dose with food.⁸

⁶ Gagne, 2011. How Many “Me-Too” Drugs Is Too Many? <https://jamanetwork.com/journals/jama/article-abstract/645581>.; Gyawali, 2017. Me-too drugs with limited benefits — the tale of regorafenib for HCC. <https://www.nature.com/articles/nrclinonc.2017.100>.

⁷ Ratain, 2018. Potential for value-based prescribing of oral oncology drugs. <https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress/Potential-for-value-based-prescribing-of-oral-oncology-drugs>.

⁸ Sinha, Gunjan, 2020. Experts Push for New Cancer Drug Dosing Recommendations. <https://undark.org/2020/12/09/cancer-drugs-less-might-be-more/>.

To understand the scale of what's at stake, consider abiraterone, a drug that is commonly prescribed to treat advanced prostate cancer. The labeled dose of abiraterone is 1,000 mg, to be taken on an empty stomach. But clinical-trials data reveal that abiraterone is absorbed 5–10 times better with food. One randomized controlled study (an international study led by The University of Chicago) of 72 patients showed particularly dramatic results⁹. Patients taking one-fourth of the typical dosage level with a low-fat breakfast achieved the same hormonal and anticancer effect as patients taking the full dose on an empty stomach! The results of this study have been incorporated into national guidelines, providing support to cost-conscious oncologists.

Another example is ibrutinib, used to treat of a number of hematological malignancies (cancers that begin in blood cells). There is evidence that the labeled dose of ibrutinib (420–560 mg daily) is no more effective than a daily dose of 140 mg.¹⁰ Moreover, patients taking the labeled dose often have to pause treatment due to the ibrutinib's toxic side effects (e.g., low blood counts, cardiac problems), an interruption which can enable the disease to become ibrutinib-resistant. Of even greater concern is the fact that ibrutinib was recently associated with over 300 cardiovascular deaths.¹¹ A lower dose of ibrutinib could not only be as or more effective than the labeled dose, it could also be significantly less toxic.

Identifying where drug dosages can be safely lowered would dramatically ease the financial burden on cancer patients. Even with Part D Medicare coverage, cancer patients are responsible for 5% of the ongoing cost of their drugs. With many of the new cancer drugs bearing a hefty monthly list price of \$10,000–\$20,000, that results in co-payments of \$500–\$1,000 per month, or \$6,000–12,000/year. Since the median American household income is just under \$70,000, this means that many cancer patients are spending at least 10% of their entire pre-tax household income on the co-pays for a single drug. And some patients receive two or more drugs in combination.

There are three options for reducing drug dosage: lowering the recommended amount per dose, administering drugs less frequently, and decreasing treatment duration. Research is needed to identify drugs where the current recommended dose may be above the optimal level and then assess which of the three options is best for dose optimization. The Federal Government has an important role to play in funding this type of research, known as “de-escalation clinical trials.” Not surprisingly, this is a kind of research that the “research-based” drug companies are not eager to support, and have generally done so only when specifically required by FDA at the time of initial drug approval.¹² As Dr. Norman Sharpless, current Director of the National Cancer

⁹ Szmulewitz, 2018. Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5941614/pdf/JCO.2017.76.4381.pdf>

¹⁰ Ratain, 2020. Ibrutinib's Cardiotoxicity—An Opportunity for Postmarketing Regulation.

<https://jamanetwork.com/journals/jamaoncology/article-abstract/2773456>.

¹¹ Salem, 2019. Cardiovascular Toxicities Associated with Ibrutinib. <https://www.jacc.org/doi/pdf/10.1016/j.jacc.2019.07.056>

¹² Lu, 2016. A survey of new oncology drug approvals in the USA from 2010

Institute and former Acting Commissioner of the Food and Drug Administration (FDA) has explained, de-escalation clinical trials are “an important topic for patients, but typically of less interest to industry [because such trials would undermine their revenue rather than increase it].”¹³

It is up to the Federal Government to correct this market failure on behalf of patients and taxpayers. An evidence-based approach to drug dosing will help millions of sick Americans financially, improve outcomes (since more people will be able to afford lower, but still effective dosages), and save billions of dollars in taxpayer-funded health-care subsidies. Indeed, funding de-escalation clinical trials is one of the most cost-effective investments that the Center for Medicare and Medicaid Innovation could make. These trials could even be self-funding if participants receive drugs through a government-funded program such as Medicare or the Veterans Health Administration. With potential drug-cost savings of 50% or more, the cost of conducting a de-escalation trial would be more than offset by the reduced drug utilization by patients in the lower-dose treatment group during that trial.

A Day One Executive Order

President Biden should issue an Executive Order (EO) in the first 100 days of his administration directing the Secretary of Health and Human Services to coordinate with all government health programs to fund de-escalation studies on priority drugs. Priority drugs would be selected based on prior dosing studies and their cost to the healthcare system. The EO should specify that de-escalation studies on an initial group of priority drugs begin within the first 6 months of the new administration. Conducting de-escalation studies on 10 drugs of high cost to the government in the first year of the next administration could yield billions of dollars in federal savings by the end of the administration’s first term, with further savings going to financially pressed states, through Medicaid, and to employers. In other words, the de-escalation study program would more than pay for itself.¹⁴ More importantly, the program would establish dose optimization as an essential and indispensable part of our country’s healthcare system—one that would cut costs for patients and taxpayers while simultaneously reducing unnecessary toxic side effects of treatment.

to 2015: a focus on optimal dose and related postmarketing activities.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4767861/pdf/280_2015_Article_2931.pdf.

¹³ Sharpless, Norman, 2018. Reflections on My First Year as NCI Director. <https://www.cancer.gov/news-events/cancer-currents-blog/2018/sharpless-first-year-nci-director>.

¹⁴ Goldstein, Daniel, Lichter, Allen, Ratain, Mark. Payer Funding of Interventional Pharmacoeconomic Studies: A New Paradigm. <https://www.healthaffairs.org/doi/10.1377/hblog20191119.302743/full/>.

Frequently Asked Questions

Q. If evidence emerges that lower drug doses are preferable to the currently recommended doses, what would prevent drug companies from just raising drug prices to compensate?

While companies could consider raising drug prices in response to external evidence that lower doses are preferable, this response would not be straightforward. The most important reason is that companies cannot market a treatment regimen that is not approved by the FDA (off label), and thus could not publicly explain price increases motivated by external research. Furthermore, there are usually competing drugs, and thus the higher price of the labeled treatment regimen would likely be much higher than that of competitors. In other words, they would lose customers because of competition. A drug price increase might also cause entities and hospitals to drop the drug from its list of recommended treatments, because of the price increase and the existence of competing drugs.

Companies could conduct post-marketing dose-optimization studies themselves, potentially resulting in a change to the labeled dose. But there may also be reasons for companies not to do so, such as method of treatment patents that cover labeled treatment regimens but not lower doses.

While none of these obstacles comprise hard legal barriers to increasing drug prices, we believe they are formidable enough to act as deterrents. Our position is supported by the FDA's requirement that Novartis conduct a postmarketing trial of lower-dose ceritinib (comparing the approved 750 mg dose to a lower 450 mg dose) to reduce gastrointestinal toxicity. The trial resulted in a label change, but no immediate price increase (per 150 mg capsule).

Q. How will people be convinced to enter clinical trials where they receive a lower dose of a drug without evidence that it will work as well as the currently recommended dose?

Many patients receiving prescription drugs are now being prescribed excessive amounts because drug doses have never been optimized. This often leads to severe side effects that can cause unnecessary complications from treatment. Once informed of the opportunity to optimize dosing and receive treatment that will likely result in lower side effects, we expect that many patients will volunteer for such trials. Indeed, patients already have. A trial of low-dose abiraterone (using a 75% dose reduction) was recently completed, and a trial of reduced-dose-frequency pembrolizumab or nivolumab is ongoing. Both trials involved volunteer patients.

Q. Is over-dosing just a problem with oncology drugs, or is this a more general problem that needs to be addressed?

We use oncology drugs as a clear example of where there are potentially serious and even deadly side effects from over-prescribing medications. However, the problem is common across the prescription drug industry.

Q. How many drugs need to be optimized? Is this just a few outliers or is this really a large problem?

A 2018 analysis showed that the majority of patent-protected oral oncology drugs are not optimally dosed.¹⁵ There is also clear evidence that the majority of expensive biologics (drugs produced by living organisms), especially immune-checkpoint inhibitors (drugs that help your immune system to recognize and attack tumors), are given in excess.

Q. How should drugs be selected for optimization trials?

Drugs should be selected based on frequency of use in the population, severity of side effects, and cost to the healthcare system.

Q. How much money could be potentially saved as a result of successful optimization trials?

The aforementioned 2018 analysis suggested that as much as 36% of the total cost of patent-protected oral oncology drugs could be saved through development of off-label treatment regimens. It is likely that similar or greater savings could be achieved by optimizing dosage of expensive biologics (drugs produced by living organisms), especially immune-checkpoint inhibitors. With the value of the current global oncology drug market estimated at \$200 billion per year, and the United States accounting for 40% of this market, potential savings could be upwards of \$25 billion per year as a result of successful optimization for oncology drugs.

Q. Isn't it going to be expensive to pay for all these trials?

Trials are essentially free if they are conducted in patients receiving government-funded healthcare (e.g., Medicare, Medicaid, services provided by the Veterans Health Administration) due the money saved on medications in the course of the trial itself. For example, a trial of low-dose ibrutinib could compare a daily dose of 140 mg (1 capsule, or \$185.23 per day) to the standard daily dose of 420 mg (3 capsules, or \$555.69 per day). Since half the patients would receive the lower dose, the cost savings for a 300-patient study would be \$55,569 per day, or \$20.3 million per year. This would more than cover the cost of conducting such a clinical trial. In fact, de-escalation trials are unique in that the larger the trial the lower the cost—not to mention

¹⁵ Ratain, 2018. Potential for value-based prescribing of oral oncology drugs. <https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress/Potential-for-value-based-prescribing-of-oral-oncology-drugs>.

that larger trials provide more statistically significant results. Furthermore, implementation of the results of one successful trial (e.g., if it was found that one-third of the standard dose of ibrutinib was safer and provided similar or improved benefit as compared to the standard dose) would pay for trials on dozens of drugs. A successful trial could also have other indirect cost savings if a lower effective dose also reduced drug toxicity.

Q. How do patients benefit from de-escalation trials?

The goal of de-escalation trials is to identify reduced drug dosages that provide the same therapeutic benefits but reduce the severity and/or duration of side effects. Successful de-escalation trials can also make treatment more convenient for patients: for instance, by reducing the frequency of drug administration or by allowing patients to avoid fasting (if food improves absorption of a lower dose).

About the Authors



Mark J. Ratain, M.D. has been a faculty member in the Department of Medicine at The University of Chicago since 1986, and is currently the Leon O. Jacobson Professor of Medicine, the Director of the Center for Personalized Therapeutics and Chief Hospital Pharmacologist. In addition, Dr. Ratain serves as the Associate Director for Clinical Sciences in the University's Comprehensive Cancer Center. Dr. Ratain's research has historically focused on the development of new oncology drugs and diagnostics, but is increasingly focused on the new discipline of interventional pharmacoeconomics. He is the recipient of awards from multiple organizations, including the American Association of Pharmaceutical Scientists, the American Society for Clinical Pharmacology and Therapeutics, the American Society of Clinical Oncology, the American College of Clinical Pharmacology, and the Pharmaceutical Research and Manufacturers Association Foundation. Dr. Ratain is on the Board of the Value in Cancer Care Consortium.



Michael Stebbins, Ph.D. is a geneticist, and public policy expert who served as the Assistant Director for Biotechnology in the Obama White House Office of Science and Technology Policy. He is currently the President of Science Advisors, a science and health consulting firm he founded in 2018 to provide science, technology, and public policy guidance to private companies, philanthropies, and non-profit organizations. While at the White House, Dr. Stebbins' work led to large initiatives across the Federal government to address antibiotic resistance, protect pollinators, improve veterans' mental health, increase access to federally funded scientific research publications and data, promote the preferential purchasing of antibiotic free meats, reform the regulatory system for biotechnology products, drive Federal purchasing of bio-based products, and improve the management of scientific collections. Dr. Stebbins previously served as the Vice President of Science and Technology for the Laura and John Arnold Foundation, science advisor to the Obama Presidential Campaign, and on the Obama White House Transition Team. He is the former director of biology policy for the Federation of American Scientists and worked for U.S. Senator Harry Reid and at the National Human Genome Research Institute. Before coming to Washington, he was a senior editor at Nature Genetics.



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