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Abuse-Deterrent Opioids and the Law of Unintended Consequences

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EXECUTIVE SUMMARY

The United States has seen a surge in deaths from overdoses of opioids, including both prescription drugs and illegal opioids such as heroin. Nonmedical users and abusers often obtain prescription opioids diverted from the legal to the illegal market. In the hope of reducing opioid use, abuse, and overdoses, policymakers have focused on developing and promoting tamper-resistant or abuse-deterrent formulations (ADFs) that render diverted opioids unusable if individuals attempt to use them for nonmedical (i.e., recreational) purposes.

Although the benefits of ADFs seem to be nonexistent, these formulations have led to real harms. ADFs have encouraged users to switch to more dangerous opioids, including illegal heroin. In at least one instance, the reformulation of a prescription opioid led to a human immunodeficiency virus (HIV) outbreak. Along the way, ADFs unnecessarily increase drug prices, imposing unnecessary costs on health insurance purchasers, taxpayers, and particularly patients suffering from chronic

pain. Like the federal government's promotion of abuse-deterrent alcohol a century ago, these efforts are producing unintended consequences, such as making legal pain relief unaffordable for many patients and possibly increasing morbidity and mortality.

Government at all levels should stop promoting ADF opioids. Congress should end or limit the ability of pharmaceutical manufacturers to impose higher costs on pain patients by using ADFs to "evergreen" their opioid patents (evergreening is a practice by which pharmaceutical manufacturers extend or renew the patent protection before the current patent expires by tweaking the formula slightly or repurposing the product). The FDA should end its policy of encouraging ADF opioids and particularly its goal of eliminating non-ADF opioids. Lawmakers should abandon efforts to require consumers to purchase coverage for costlier ADF opioids and should instead allow insurers to steer medical users of these products toward cheaper, non-ADF generic formulations.

“To reduce opioid abuse, policymakers have focused on tamper-resistant or abuse-deterrent formulations that render diverted opioids unusable if used for nonmedical purposes.”

INTRODUCTION

The United States has seen a surge in deaths from overdoses of opioids, including both prescription and illegal opioids such as heroin. Nonmedical users and abusers often obtain prescription opioids diverted from the legal to the illegal market. In the hope of reducing opioid use, abuse, and overdoses, policymakers have focused on developing and promoting tamper-resistant or abuse-deterrent formulations (ADFs) that render diverted opioids unusable if individuals attempt to use them for nonmedical (i.e., recreational) purposes. Congress allows pharmaceutical manufacturers in effect to extend the patent life of opioids by introducing ADFs. The U.S. Food and Drug Administration (FDA) encourages manufacturers to develop tamper-resistant opioids.¹ Some state legislatures have required insurance plans to cover the cost of those reformulated drugs.²

Little evidence suggests that abuse-deterrent formulations of opioids are having the intended effect of reducing the opioid overdose death rate, and strong evidence suggests that they are contributing to the rise in heroin use and overdoses. In some cases, ADFs may result in nonmedical users switching from snorting or inhaling the substance to injecting it intravenously. That method of administration carries all the risks associated with sharing or reusing dirty needles, including the spread of hepatitis and human immunodeficiency virus (HIV).³ ADFs are also contributing to a rise in the price of pain medicine for patients receiving prescriptions from health care practitioners.

Federal and state policymakers should stop promoting abuse-deterrent opioids. Like the federal government's promotion of abuse-deterrent alcohol a century ago, these efforts are producing unintended consequences, such as making legal pain relief unaffordable for many patients and possibly increasing morbidity and mortality.

ABUSE-DETERRENT ALCOHOL

Opioids are not the first example of government trying to reformulate lawful products to

prevent people from putting those products in their bodies without government approval. Today's efforts to promote abuse-deterrent opioids are reminiscent of government efforts to promote abuse-deterrent alcohol during the 1920s.

On January 17, 1920, the Volstead Act banned intoxicating beverages and the manufacture, sale, or transport of intoxicating liquor (i.e., ethanol). The act allowed the sale of ethanol for scientific and commercial uses, however, such as the production of fuel, dye, paints, and other lawful manufactures. As with prescription opioids, bootleggers inevitably diverted commercial ethanol and sold it on the black market.

Initially, the federal government required commercial ethanol to be denatured by ordering manufacturers to add toxic or unappetizing chemicals so people could not drink it. But bootleggers were able to redistill the ethanol to make it potable again. By the middle of the 1920s, the U.S. Treasury Department, which enforced Prohibition laws, estimated that bootleggers had diverted and redistilled 60 million gallons of commercial-use ethanol per year to feed the demand.⁴

In 1926, the Treasury Department attempted to thwart the bootleggers' ability to repurify denatured alcohol by ordering the denaturing ingredients to include “4 parts methanol (wood alcohol), 2.25 parts pyridine bases, 0.5 parts benzene to 100 parts ethyl alcohol.” Other additives included kerosene and brucine (related to strychnine).⁵ Methanol damages the optic nerve; drinking it causes blindness. The effects of these additives were well known. In January 1927, *Time* magazine reported, “Three ordinary drinks of this [denatured alcohol] may cause blindness.”⁶

Some officials protested this deliberately harmful policy. In a 1926 press conference, New York City medical examiner Charles Norris exclaimed, “The government knows it is not stopping drinking by putting poison in alcohol, yet it continues the poisoning process.” He pointed out that the harmful effects of this abuse deterrence fell disproportionately on the poor because they could not afford better

whiskey and “deal in low grade stuff.”⁷ Senator James Reed (D) of Missouri argued, “Only one possessing the instincts of a wild beast would desire to kill or make blind the man who takes a drink of liquor, even if he purchased it from one violating the Prohibition statutes.”⁸

The inhumanity of this policy did not deter Prohibition advocates. Seymour M. Lowman, the Treasury official in charge of enforcing Prohibition, reportedly defended the policy by arguing that it was only people on the fringes of society who resorted to alcohol on the black market that the government was poisoning to death, and if the result was a more sober America, “a good job will have been done.”⁹ The abuse-deterrence program did not end until the repeal of Prohibition in 1933. By then, the abuse-deterrent-alcohol program alone had caused an estimated 10,000 deaths.¹⁰

Those who advocated government force to prevent adults from ingesting alcohol tolerated the casualties of that policy. Those who advocate using government force to prevent adults from putting opioids into their bodies may be inflicting casualties today by promoting or mandating abuse-deterrent formulations of opioids.

THE BIRTH OF ABUSE-DETERRENT FORMULATIONS

Today’s bootleggers may divert prescription opioids to the black market at any point in the supply chain—from the wholesaler, to the hospital dispensary, to the family medicine cabinet.¹¹ Policymakers therefore have sought ways to reformulate opioids to make them unusable no matter where the diversion occurs. Reformulation can mean making tablets harder to crush, dissolve, chew, or inhale. It can also involve combining the opioid with an opioid antagonist to block its rewarding effects.

The first FDA-approved ADF of an opioid was OxyContin in 2010. Although the opioid oxycodone had been in clinical use since 1916, Purdue Pharmaceuticals developed the long-acting variant, OxyContin, in 1996. This preparation contained a much higher concentration of oxycodone in a controlled-release tablet

that patients could take every 12 hours for control of chronic pain. Because of the greater concentration of oxycodone, bootleggers diverted a great amount of OxyContin to the illegal market for recreational use. Often dubbed “hillbilly heroin,” users would crush it into a fine powder and snort or chew it, or dissolve the powder in water and inject it intravenously.

In 2010, Purdue released a reformulation of OxyContin that is resistant to crushing, forms a gel not easily injected when dissolved in solutions, and resists extraction with solvents. After receiving the ADF designation from the FDA, Purdue stopped manufacturing the original formulation of OxyContin and only manufactured and sold the reformulated version. All OxyContin on the market today is of the reformulated ADF variety.¹²

Since 2010, the FDA has approved several new ADF opioids in addition to OxyContin:

- Suboxone is a combination of buprenorphine (a potent opioid with properties similar to methadone) and naloxone. Suboxone treats addiction in a way similar to methadone. Naloxone is an opioid antagonist; it blocks opioids from reaching the body’s opioid receptors. The body’s intestinal walls do not absorb naloxone, so it has little effect when patients ingest it orally in conjunction with the buprenorphine. But if users crush and inject the suboxone pill, the naloxone blocks the opioid receptors. This method of using suboxone may therefore lead to withdrawal symptoms.¹³
- Hysingla ER, Vantrela ER, and Zohydro ER are extended-release reformulations of long-acting, controlled-release hydrocodone that prevent crushing and injecting in ways similar to reformulated OxyContin.
- Embeda, MorphaBond ER, and Arymo ER are combinations of extended-release oral morphine and naltrexone, an opioid antagonist, based on a strategy similar to that of Suboxone.

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- Oxaydo and Roxybond are ADFs of oxycodone. If dissolved, they become gelatinous and unsuitable for injecting. If users crush and snort them, they cause severe nasal irritation—what Oxaydo’s manufacturer calls “nasal burning.”¹⁴
- Xtampza ER is a recently approved, tamper-resistant, long-acting oxycodone ADF, similar to OxyContin but with a different proprietary means of deterring crushing and chewing.
- Opana ER is an ADF of oxymorphone. It also employs crush-resistant technology, resists extraction with solvents, and becomes a gel if dissolved in water. Opana ER is to date the only ADF opioid that pharmaceutical manufacturers have pulled from the market at the request of the FDA (see below).¹⁵

Importantly, ADFs do nothing to prevent nonmedical users from swallowing these pills with a glass of water, which is their intended form of administration.

DO ABUSE-DETERRENT FORMULATIONS DETER ABUSE OR JUST ENCOURAGE USERS TO SWITCH TO HEROIN?

Several studies question the efficacy of reformulated products and the usefulness of encouraging their continued development.¹⁶ Data show that in recent years, the overdose death rate attributable to prescription opioids has stabilized, while the death rate from heroin has increased.¹⁷ In 2015, deaths due to heroin overdose eclipsed those from prescription opioids for the first time.¹⁸ Those trends suggest that, to the extent that ADFs have made prescription opioids harder to use, those users have simply switched to heroin, which former Centers for Disease Control and Prevention director Thomas Frieden estimated is available for one-fifth the street price of prescription opioids.¹⁹

Indeed, several studies provide evidence that the introduction of ADFs has

primarily led nonmedical users to switch from their prescription opioid of choice to cheaper, easier-to-use heroin. Because of the popularity of OxyContin on the illegal market and because, since 2010, only the reformulated product has been available, much research exists on that ADF’s effects.

Numerous studies have questioned the benefits of tamper-resistant OxyContin. Studies in *JAMA Psychiatry* and the *Canadian Medical Association Journal* found that introduction of the abuse-deterrent form did lead to a reduction in OxyContin use, but the ADF may have contributed to a rise in heroin abuse, and it had no effect on the opioid overdose rate.²⁰

A 2017 study by researchers at the RAND Corporation and the University of Pennsylvania noted that efforts to disrupt the supply of OxyContin for abuse “may have the unintended consequence of increasing the use of substitute drugs, including heroin.” States with higher levels of OxyContin misuse before 2010 (when the ADF replaced original OxyContin) experienced a greater drop in OxyContin misuse but also a larger increase in heroin deaths following the reformulation. The researchers saw minimal evidence of a “differential reduction in overall opioid-related deaths, potentially due to substitution towards other opioids, including more harmful synthetic opioids such as fentanyl.”²¹

In June 2017, economists William Evans and Ethan Lieber of Notre Dame University and Patrick Power of Boston University revealed in a working paper an even more direct correlation between the replacement of OxyContin with its abuse-deterrent formulation and the increase in heroin use. They found that OxyContin consumption stopped rising with the reformulation in August 2010 and heroin deaths began to climb the following month:

When we combine heroin and opioid deaths together, we find no evidence that total heroin and opioid deaths fell at all after the reformulation—there appears to have been one-for-one substitution of heroin deaths for opioid deaths.

“The risks that abuse-deterrent formulations introduce may actually surpass the risks of opioid use and abuse.”

Thus it appears that the intent behind the abuse-deterrent reformulation of OxyContin was completely undone by changes in consumer behavior.²²

A THREAT TO PUBLIC HEALTH?

Because ADFs appear to encourage opioid users to switch to heroin, the risks that ADFs introduce may actually surpass the risks of opioid use and abuse. Illegal heroin increases the risks of overdose, dangerous additives, and disease transmission.

ADFs can harm patients even when they do not switch to heroin. In 2012, Endo Pharmaceuticals reformulated its drug Opana ER, an extended-release hydromorphone, to make it resistant to crushing and snorting. Consequently, many abusers switched to injecting the drug. In early 2015, a cohort of roughly 190 people tested positive for HIV in Scott County, Indiana; it was the largest outbreak in Indiana history. Public health officials tied the outbreak to the sharing of dirty needles to inject the ADF of Opana ER.²³

The FDA responded by asking Endo Pharmaceuticals to take Opana ER off the market. In announcing the request, the director of the FDA's Center for Drug Evaluation and Research, Janet Woodcock, said, “The abuse and manipulation of reformulated Opana ER by injection has resulted in a serious disease outbreak. When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market.”²⁴ The FDA stated that should Endo Pharmaceuticals fail to remove the product from the market voluntarily, the agency would take formal steps to require its removal. The manufacturer complied with the agency's request in July 2017.

The FDA recognized and responded to the unintended consequences of this ADF, once they became visible. The agency nevertheless tolerates dangerous unintended consequences of ADFs, including those associated with greater heroin use, because they are less visible—and it even tolerates some harms of

ADFs, including withdrawal symptoms and severe nasal irritation, because policymakers and pharmaceutical manufacturers *intend* those harms.

ABUSE-DETERRENT OPIOIDS AND HEALTH CARE SPENDING

Policymakers' demand for ADFs creates large profit opportunities for pharmaceutical manufacturers and imposes significant costs on patients suffering from chronic pain. The patent protections for many of the original opioid preparations have expired. When that occurs, competition from generic drugs reduces prices for opioids—and cuts into the profits of drug companies that first brought those drugs to market.

ADFs provide pharmaceutical manufacturers with an opportunity to restore those lost profits by extending or renewing the patent protection they had enjoyed before patent expiration, a strategy known as “evergreening.” According to one study, evergreening is a growing practice: “Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. Every year, at least 74 percent of the drugs associated with new patents in the FDA's records were not new drugs coming on the market, but existing drugs.”²⁵ Another study found that patents filed for new formulations of already patented drugs “add an average of 6.5 years to patent life.”²⁶ The new abuse-deterrent products receive new patents, are not available in generic form, and therefore can fetch higher prices.

The FDA is actively encouraging pharmaceutical manufacturers to evergreen their opioid products by developing new ADFs.²⁷ In April 2015, the FDA published “Guidelines for Industry” to facilitate the development of ADFs.²⁸ In July 2017, FDA commissioner Scott Gottlieb announced his support for transitioning to a market dominated by abuse-deterrent opioids.²⁹ Transitioning to an all-ADF market could eliminate any generic competition, resulting in higher prices and spending. Pharmaceutical manufacturers face strong economic incentives to develop new ADFs of

“In at least one instance, the reformulation of a prescription opioid led to an HIV outbreak.”

opioids, to receive FDA certification of their ADF products, and to promote ADFs as a tool for combating opioid addiction and overdoses.

State laws mandating that consumers purchase health insurance coverage of ADF opioids represent another profit opportunity for brand-name opioid manufacturers. At present, many health insurance plans cover only the older opioids that do not contain abuse deterrents. Patients who wish to use abuse-deterrent opioids often have to pay very high prices. In response, many state legislatures have considered mandating that health insurance plans cover ADFs, and some have done so.³⁰

Mandating coverage of abuse-deterrent opioids would impose significant and unwanted costs on consumers and taxpayers. The University of Pittsburgh Medical Center Health Plan estimates that mandating coverage of ADFs could cost the plan \$400 million annually.³¹ The company points to data from the Department of Veterans Affairs (VA) showing that in fiscal year 2016 abuse-deterrent opioids accounted for 1.9 percent of opioids dispensed, yet accounted for 37 percent of opioid spending by the VA.

Other nations have rejected ADFs as useless and costly. Like the United States, Canada has a severe opioid overdose problem, and ranks second only to the United States in per capita opioid consumption.³² Yet in 2016, Health Canada, the government agency that administers the Canadian health system, decided against moving toward an all abuse-deterrent opioid formulary:

Specifically, requiring tamper-resistant properties on all legitimate preparations of controlled-release oxycodone would have served to eliminate certain lower cost drugs from the market, increasing costs for patients and the health system, while having little to no effect in the fight against problematic opioid use.³³

Mandatory coverage of ADF opioids would not be the first instance of state-mandated coverage of medical treatments that do more

harm than good. State legislatures, subject to popular and political forces, have mandated insurance coverage for treatments in the past that have ultimately proved harmful. In the 1990s, for example, some states required consumers to purchase coverage for an experimental, expensive, and highly toxic breast-cancer treatment called high-dose chemotherapy with autologous bone marrow transplant. The treatment involves harvesting the patient's bone marrow, administering essentially lethal doses of chemotherapy, and then reinfusing the patient's bone marrow to restart her immune system. The treatment proved no more effective than standard chemotherapy, meaning it subjected breast-cancer patients to greater suffering for no clinical benefit. Under pressure from patient advocacy groups, states—including Massachusetts and Minnesota—nevertheless required insurers to cover the procedure.³⁴

GOVERNMENT SHOULD STOP PROMOTING ADF OPIOIDS

The goal of ADFs is to make prescription opioids unusable to people seeking to use or abuse them for nonmedical purposes via chewing, snorting, or injecting. Yet ADF opioids do not appear to have reduced opioid use or overdoses. Despite the introduction of ADF opioids in 2010—including the complete replacement of OxyContin, one of the most popularly abused opioids, with its ADF—opioid overdose death rates continue to rise year after year.³⁵ Indeed, ADF opioids arguably cannot reduce nonmedical use because users can always take them with a glass of water.

Although the benefits of ADFs appear to be nonexistent, they have led to real harms. ADFs have encouraged users to switch to more dangerous opioids, including illegal heroin. In at least one instance, the reformulation of a prescription opioid led to an HIV outbreak. Along the way, ADFs unnecessarily increase drug prices, imposing unnecessary costs on health insurance purchasers, taxpayers, and particularly patients suffering from chronic pain.

The evidence shows that ADF opioids are an ineffective and harmful approach to reducing opioid overdoses. Government at all levels should stop promoting them. Congress should end or limit the ability of pharmaceutical manufacturers to impose higher costs on pain patients by using ADFs to evergreen their opioid patents. The FDA should end its policy of encouraging ADF opioids, particularly its goal of eliminating non-ADF opioids. Ideally, the agency should adopt a position of skepticism. At the least, it should be neutral on the issue. Lawmakers should abandon efforts to require consumers to purchase coverage for costlier ADF opioids and should instead allow insurers to steer medical users of these products toward cheaper, non-ADF, generic formulations.

NOTES:

1. U.S. Dept. of Health and Human Services, Food and Drug Administration, "FDA Issues Final Guidance on the Evaluation and Labeling of Abuse-Deterrent Opioids," April 1, 2015, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm>.
2. Andy Wagner, "States Have Stalled on Potential Opioid Abuse Solution: Deterrent Formulation Drugs," *MultiState* (blog), April 24, 2017, <https://www.multistate.us/blog/state-efforts-have-stalled-on-potential-opioid-abuse-solution-deterrent-formulation-drugs>.
3. Marisa Crane, "Dangers of Shooting Up," *DrugAbuse.com*, <http://drugabuse.com/library/dangers-of-shooting-up/>.
4. Deborah Blum, "The Chemist's War," *Slate*, February 19, 2010, http://www.slate.com/articles/health_and_science/medical_examiner/2010/02/the_chemists_war.html.
5. Lily Rothman, "The History of Poisoned Alcohol Includes an Unlikely Culprit: The U.S. Government," *Time*, January 14, 2015, <http://time.com/3665643/deadly-drinking/>.
6. *Ibid.*
7. Blum, "The Chemist's War."
8. *Ibid.*
9. Rothman, "The History of Poisoned Alcohol."
10. Blum, "The Chemist's War."
11. James A. Inciardi et al., "Mechanisms of Prescription Drug Diversion among Drug-Involved Club- and Street-Based Populations." *Pain Medicine* 8, no. 2 (2007): 171–83, <https://doi.org/10.1111/j.1526-4637.2006.00255.x>.
12. William N. Evans et al., "How the Reformulation of OxyContin Ignited the Heroin Epidemic," working paper, Departments of Economics, University of Notre Dame and Boston University, June 1, 2017, p. 5, <https://www3.nd.edu/~elieber/research/ELP.pdf>.
13. "Suboxone vs. Subutex: What's the Difference? (And Which One Is Right for You?)," CRC Health, <http://www.crchealth.com/addiction/heroin-addiction-treatment/heroin-detox/buprenorphine-suboxone-vs/>.
14. "Egalet Announces Commercial Launch of OXAYDO™, the First and Only Immediate-Release Oxycodone Designed to Discourage Intranasal Abuse, and Launch of IMPACT-Rx, a Patient Access Initiative," news release, Egalet Corporation, September 9, 2015, <https://www.prnewswire.com/news-releases/egalet-announces-commercial-launch-of-oxaydo-the-first-and-only-immediate-release-oxycodone-designed-to-discourage-intranasal-abuse-and-launch-of-impact-rx-a-patient-access-initiative-300139545.html>.
15. Other ADFs include Exalgo, a crush- and extraction-resistant form of the opioid hydromorphone; Targiniq ER, a combination of extended-release hydrocodone and naloxone; and Troxyca ER, a combination of extended-release oxycodone and naltrexone.

- “Clinical Charts: Opioids with Abuse Deterrent Properties,” *Monthly Prescribing Reference*, August 10, 2017, <http://www.empr.com/clinical-charts/opioids-with-abuse-deterrent-properties/article/333126/>.
16. Institute for Clinical and Economic Review, “Final Evidence Report—Abuse-Deterrent Formulations of Opioids: Effectiveness and Value,” August 8, 2017, https://icer-review.org/wp-content/uploads/2016/08/NECEPAC_ADF_Final_Report_08_08_17.pdf.
17. Rose A. Rudd et al., “Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014,” *CDC Morbidity and Mortality Weekly Report* 64, no. 50 (January 1, 2016): 1378–82, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm>.
18. Sarah Frostenson, “Opioid Overdoses Are Climbing. But Prescription Painkillers Aren’t Driving Them Anymore,” *Vox*, April 1, 2017, <https://www.vox.com/science-and-health/2017/4/1/15115380/prescription-painkiller-heroin-deaths>.
19. Richard Harris, “Heroin Use Surges, Especially among Women and Whites,” *NPR*, July 7, 2015, <http://www.npr.org/sections/health-shots/2015/07/07/420874860/heroin-use-surges-especially-among-women-and-whites>.
20. Theodore J. Cicero and Matthew S. Ellis, “Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin,” *JAMA Psychiatry* 72, no. 5 (2015): 424–30, doi: 10.1001/jamapsychiatry.2014.3043; and Pamela Leece et al., “Tamper-Resistant Drugs Cannot Solve the Opioid Crisis,” *Canadian Medical Association Journal* 187, no. 10 (2015): 717–18, doi: 10.1503/cmaj.150329.
21. Abby Alpert et al., “Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids,” NBER Working Paper no. 23031, January 2017, <http://www.nber.org/papers/w23031>.
22. William N. Evans et al., “How the Reformulation of OxyContin Ignited the Heroin Epidemic,” working paper, June 2017, p. 5, <https://www3.nd.edu/~elieber/research/ELP.pdf>.
23. Tom Dreisbach, “How a Painkiller Designed to Deter Abuse Helped Spark an HIV Outbreak,” *NPR*, April 1, 2016, <https://www.npr.org/sections/health-shots/2016/04/01/472538272/how-a-painkiller-designed-to-deter-abuse-helped-spark-an-hiv-outbreak>; and Mike Riggs, “Opana ER and the Failure of the Tamper-Proof Drug Model,” *Reason, Hit and Run Blog*, June 9, 2017, <http://reason.com/blog/2017/06/09/opana-er-and-the-failure-of-the-tamper-p>.
24. Riggs, “Opana ER and the Failure of the Tamper-Proof Drug Model.”
25. Robin Feldman and Connie Wang, “May Your Drug Price Be Ever Green,” Social Science Research Network, December 14, 2017, p. 47, <https://ssrn.com/abstract=3061567>.
26. Amy Kapczynski et al., “Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of ‘Secondary’ Pharmaceutical Patents,” *PLOS ONE* 7, no. 12 (2012): e49470, <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049470>.
27. U.S. Dept. of Health and Human Services, Food and Drug Administration, “FDA Opioids Action Plan,” July 11, 2017, <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm>.
28. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, “Abuse-Deterrent Opioids—Evaluation and Labeling,” April 2015, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>.
29. U.S. Dept. of Health and Human Services, Food and Drug Administration, “Statement from FDA Commissioner Scott Gottlieb, M.D., on National Academies of Sciences, Engineering, and Medicine Report on Pain Management and Prescription Opioid Abuse,” July 13, 2017, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm566958.htm>.
30. Andy Wagner, “States Have Stalled on Potential Opioid Abuse Solution: Deterrent Formulation Drugs,” *MultiState* (blog), April 24, 2017, <https://www.multistate.us/blog/state-efforts-have-stalled-on-potential-opioid-abuse-solution-deterrent-formulation-drugs>.
31. Chronis Manolis et al., “Mandating Coverage of Abuse-Deterrent Opioids Would Be a Costly Distraction from More Effective Solutions,” *Health Affairs Blog*, May 26, 2017, <http://healthaffairs.org/blog/2017/05/26/mandating-coverage-of-abuse-deterrent-opioids-would-be-a-costly-distraction-from-more-effective-solutions/>.

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32. Laura Kane, "Canada Ranked Second in World for Per Capita Opioid Use," *Canadian Press*, August 24, 2016, <http://globalnews.ca/news/2899965/canada-ranked-second-in-world-for-per-capita-opioid-use/>.
33. Pat Anson, "Canada: Abuse Deterrent Opioids Too Expensive," *Pain News Network*, April 12, 2016, <https://www.painnewsnetwork.org/stories/2016/4/12/canada-abuse-deterrent-opioids-too-expensive>.
34. Michelle M. Mello and Troyen A. Brennan, "The Controversy Over High-Dose Chemotherapy with Autologous Bone Marrow Transplant for Breast Cancer," *Health Affairs* 20, no. 5 (2001): 101–17, <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.20.5.101>; and Peter D. Jacobson and Shannon Brownlee, "The Health Insurance Industry and the Media: Why the Insurers Aren't Always Wrong," *Houston Journal of Health Law & Policy* 5 (2004): 235–67, https://www.law.uh.edu/hjhlp/volumes/Vol_5_2/Jacobson.pdf.
35. Centers for Disease Control and Prevention, "Drug Overdose Death Data," last updated December 16, 2016, <https://www.cdc.gov/drugoverdose/data/statedeaths.html>.

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