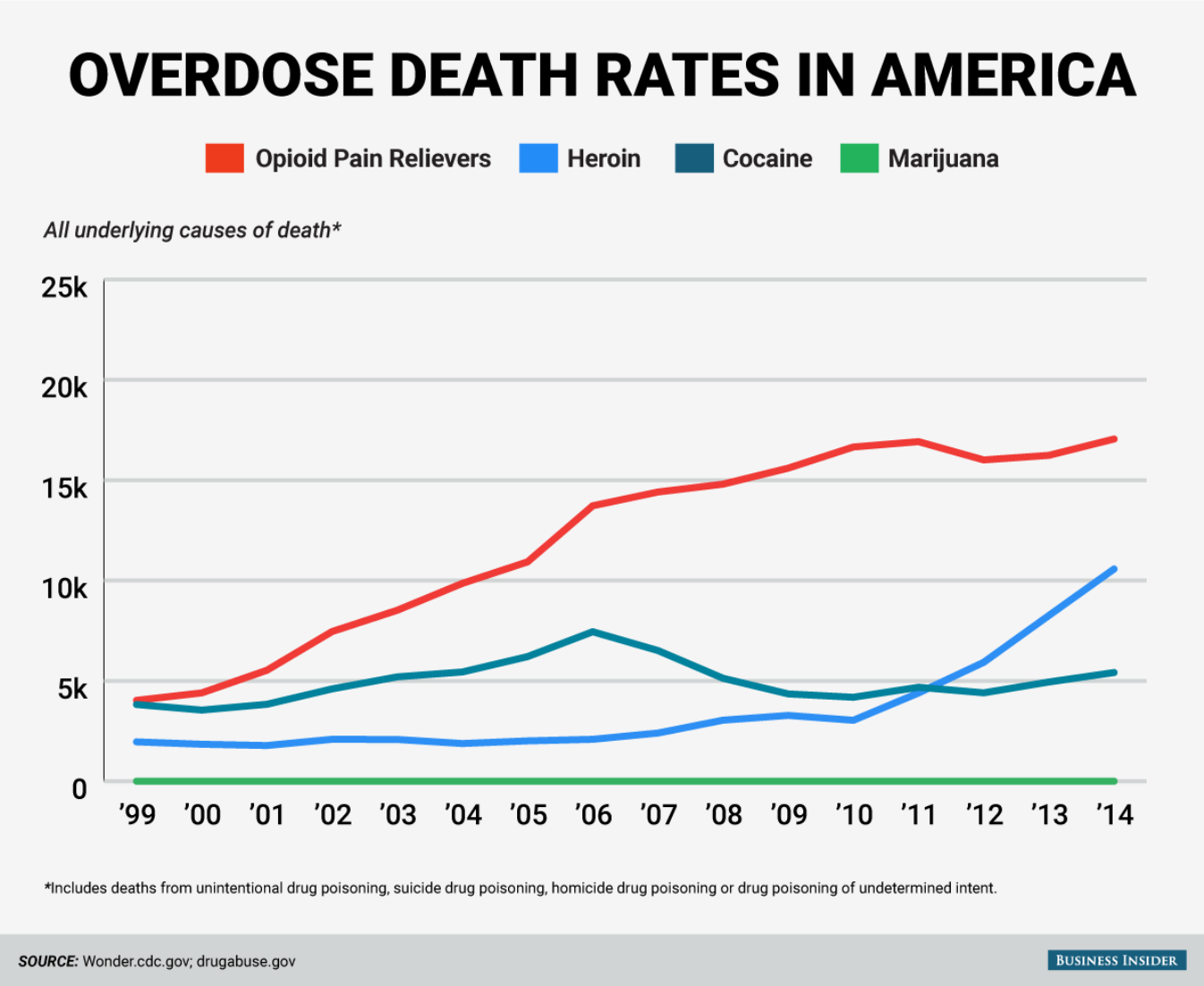
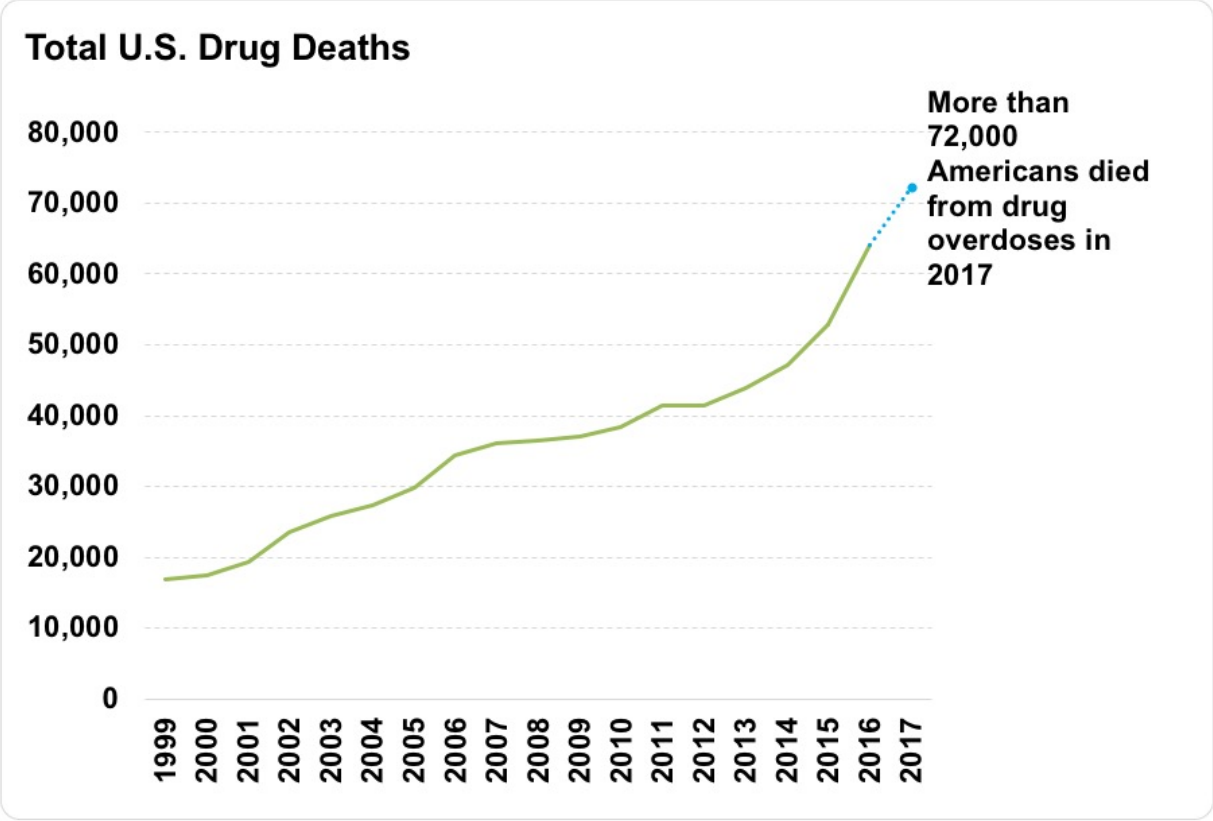
Session 10

The Prescription Opiate Crisis
November 28, 2018



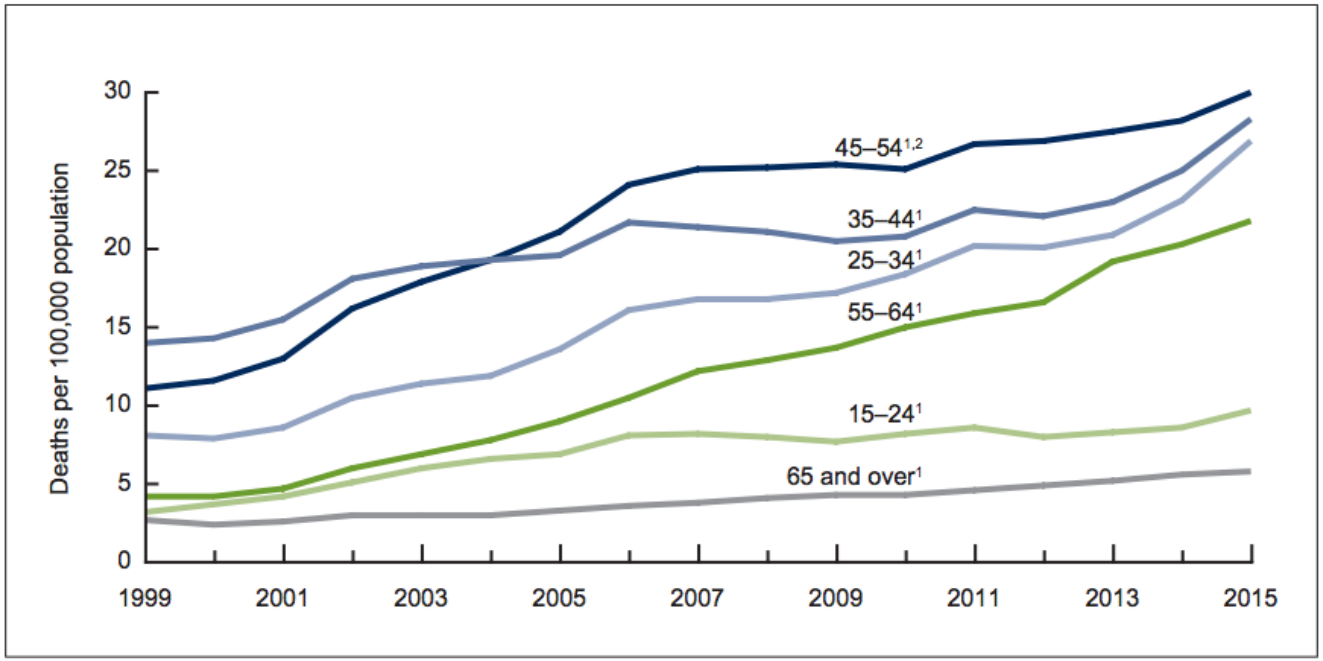
The opioid crisis is one of the major health crises of our time. Between 1999 and 2016, there have been over 200,000 overdose deaths **(https://www.cdc.gov/drugoverdose/data/overdose.html)** in America due to prescription opioids. This is less than the number of deaths due to AIDs (660,000) or by gunshot (533,000 from 1999-2015), but the rate of overdose deaths is still accelerating and, with over 72,000 overdose deaths **(https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)** of all types last year, it is the leading cause of death for Americans age 50 and under, and is more than the deaths from gunshot and auto accident combined.



https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates **(https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)**

Unlike other drug epidemics which emerged mostly among younger people, the opioid crisis has disproportionately affected people in their prime to middle age: 35-55 years old, often as a result of workplace injuries **(https://www.bostonglobe.com/metro/2018/08/08/study-links-opioid-deaths-workplace-injuries/RL0MF2br6JHDDgyiPpMYfM/story.html?s_campaign=breakingnews:newsletter)** leading to opioid prescription.

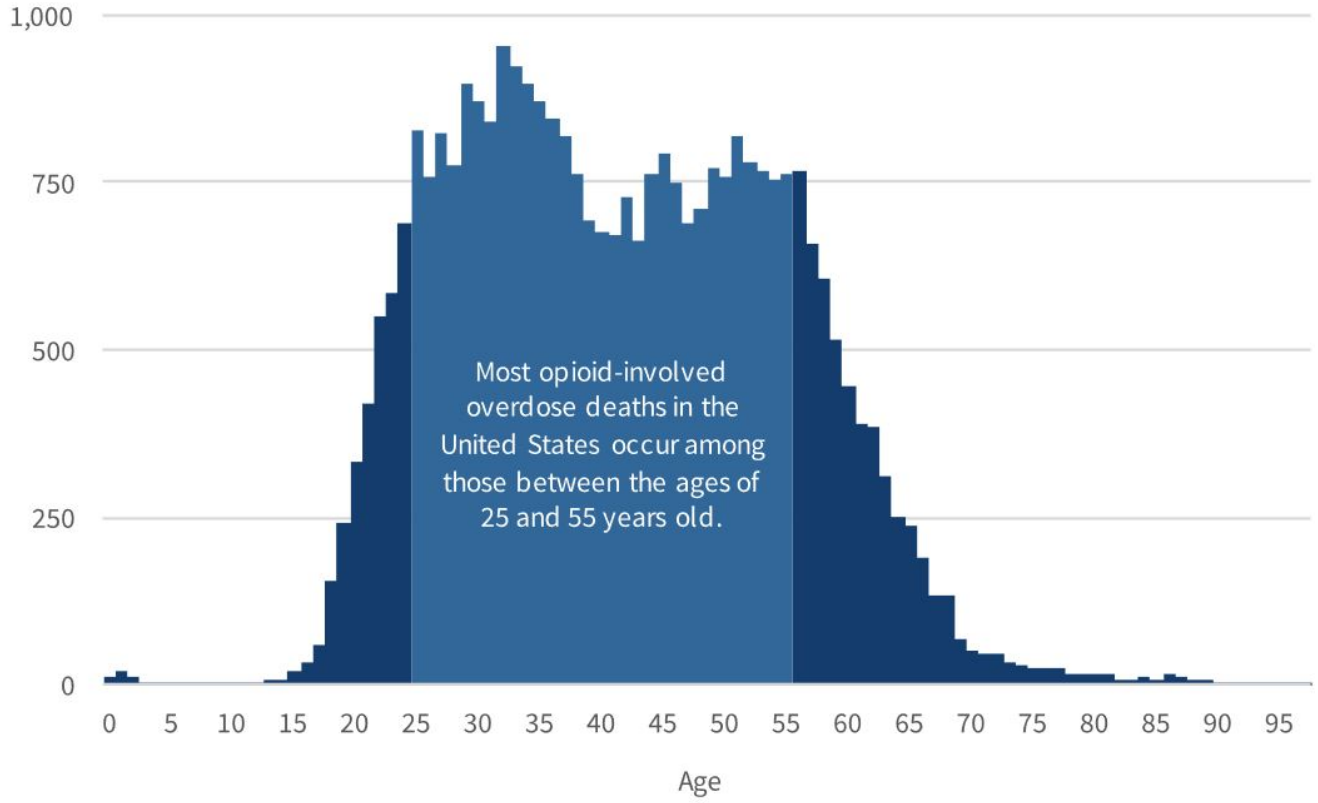
Figure 2. Drug overdose death rates, by age group: United States, 1999–2015



[1]Significant increasing trend, $p < 0.005$.
[2]Rate for age group 45–54 in 2015 was significantly higher than for any other age group, $p < 0.001$.
NOTES: Deaths are classified using the *International Classification of Diseases, Tenth Revision*. Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db273_table.pdf#2.
SOURCE: NCHS, National Vital Statistics System, Mortality.

But it is not just the middle aged who are dying; death rates among young people are increasing rapidly as well:

Figure 2. Opioid-involved Overdose Deaths by Age in 2015
(Number of deaths)



Source: CDC Wonder database, multiple cause of death files

https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf **(https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf)**

Given state variation in death reporting, these estimates may undercount the opioid death rates by up to 25% **(https://www.sciencedirect.com/science/article/pii/S0749379717303136)** . And with 4.3 million people using prescription opioids recreationally **(https://www.samhsa.gov/atod/opioids)** , and with close to 2 million people addicted to them, the problem is likely to get worse.

Purdue Pharma

While it may be true that success has many fathers while failure is an orphan, the failures of the opioid crisis are so monumental that they required many fathers. The DEA, FDA and Justice department did not do their job of protecting the American people. The medical establishment and the American Medical Association played a leading role in causing the crisis. But no organization was more responsible for the crisis than Purdue Pharma, the maker of Oxycontin. And the grandfather of the crisis was the patriarch of the Sackler family which owns Purdue Pharma, Arthur Sackler. The story is well told in the New Yorker article, The **Family That Built an Empire of Pain (https://canvas.harvard.edu/courses/41939/files/6268965/download?wrap=1)**  **(https://canvas.harvard.edu/courses/41939/files/6268965/download?wrap=1)**, as well as the prescient book by Barry Meier, Pain Killer: An Empire of Deceit and the Origin of America's Opioid Epidemic **(https://www.amazon.com/Pain-Killer-Empire-Americas-Epidemic/dp/0525511105/ref=sr_1_1?ie=UTF8&qid=1534600303&sr=8-1&keywords=barry+meier+pain+killer)**, from which much of this section is borrowed.

Arthur Sackler, like his two brothers Raymond and Mortimer, was a psychiatrist who with his brothers published over 150 scientific papers while working at the Creedmoor Psychiatric Center in Queens. In 1942 he took a copywriting job with Williams Douglas McAdams, a small ad agency specializing in the medical field. He proved so adept that he eventually purchased the agency. Arthur Sackler is widely considered to be the father of pharmaceutical marketing, having innovated targeted advertising for doctors, endorsements by prominent doctors, direct salesmen targeting doctors with research papers and freebie giveaways, and paid speakers, dinners and junkets disguised as continuing medical education courses. In the 1960's Sackler made a fortune by taking on the campaign for Librium and Valium, two nearly identical anti-anxiety tranquilizers owned by Hoffman-LaRoche. Both drugs are benzodiazepines, highly addictive drugs which induce dependence in 47% **(https://link.springer.com/article/10.1007/s00213-002-1376-8)** of those taking it for one month or more. Nevertheless, Sackler marketed the drugs in an unprecedented advertising campaign to general practitioners for tension, anxiety, muscle spasms, worries, rapid pulse, faintness, breathlessness, missed periods, hot flashes, fear, and depression. As the New Yorker article said, *"One campaign encouraged doctors to prescribe Valium to people with no psychiatric symptoms whatsoever: "For this kind of patient—with no demonstrable pathology—consider the usefulness of Valium."* Valium became the first drug to achieve annual sales of $100 million and also the first to reach sales of $1 billion, and Sackler became very rich. Sackler and his brothers expanded into a variety of privately held mutually reinforcing businesses. They owned a newspaper, Medical Tribune which was distributed to doctors and used to pitch their products, a journal article reprint company called MD Publications which was used as a conduit to bribe an FDA examiner, a prescription-tracking company called IMS Health that pharmaceutical companies use to learn about the drugs a doctor is prescribing, so that sales reps can tailor their pitches, and several

drug companies including Purdue Frederick which sold Senecot laxatives and Betadine antiseptics. In the late 1970's another Sackler family business, Napp Pharmaceuticals acquired the rights to a sustain release morphine pill, MS Contin, which was introduced in England in 1980 and through Purdue Pharma in the United States in 1984. The drug was targeted to cancer patients and people just out of surgery and the benefit of the time release was that the dose would last from 8 to 12 hours, enough to sleep through the night. MS Contin was the largest success for Purdue Pharma, achieving annual sales of several hundred million dollars. However the problem was that the patent was due to expire in the late 1980's. Arthur expired prior to the patent, in 1987, and Purdue, under the direction of Mortimer and Raymond Sackler together with Raymond's son Richard, came up with a new drug, OxyContin. OxyContin used the same time release coating as MS Contin, but it wrapped around oxycodone instead of morphine. The two drugs are very similar, but while oxycodone is 50% stronger than morphine, doctors tended to view it as weaker **(https://www.esquire.com/news-politics/a12775932/sackler-family-oxycontin/)**, and thus safer, since it is used in Percocet and Percodan with only 5 milligrams oxycodone, combined with acetaminophen and aspirin respectively. Also, some doctors confused oxycodone with codeine, which is only 1/10 as strong as morphine. But the biggest difference between MS Contin and OxyContin was in its marketing. The market for patients with cancer pain is relatively small, but 10% of all adults suffer from chronic pain **(https://journals.lww.com/pain/Fulltext/2008/09150/Prevalence_and_characteristics_of_opioid_use_in.6.aspx)**. As Barry Meier says, *"From the beginning, company executives planned to turn OxyContin into the first powerful narcotic ever mass-marketed for common conditions such as lower-back pain, arthritis, surgical pain, fibromyalgia, dental pain, and pain resulting from broken bones, sports injuries, and trauma. Simply put, the company's plan was to expand the use of long-lasting opioids from cancer wards into the mainstream of medicine by convincing thousands of family doctors, general practitioners, dentists, and anyone else who held a prescribing pen that OxyContin was safe and wouldn't lead to abuse and addiction by patients."* As Richard Sackler declared, *"OxyContin is our ticket to the moon."*

In order to market to general practitioners, Purdue would somehow have to convince them that OxyContin would not lead to addiction. The FDA helped Purdue with this key selling point by allowing the label to say *'Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.'* The rationale was that if the drug was absorbed into the bloodstream more slowly, it should create less of a high. The idea was disputed within the FDA, but the FDA examiner, Curtis Wright IV, defended the claim with no evidence. OxyContin was approved by the FDA in late 1995, and in 1998 Curtis Wright, the former FDA examiner was hired by Purdue as an executive medical director with first year compensation of $379,000.

The Pendulum Swings: from Opiophobia to Opiophilia

During much of the 20th century many doctors were reluctant to prescribe opiates, a view which has been criticized as "opiophobia (https://www.ncbi.nlm.nih.gov/pubmed/2870626) ", defined as the irrational and undocumented fear that appropriate use will lead patients to become addicts. Doctors were also cautious due to fear of overdose, fear of Harrison Act style government sanctions, and ignorance regarding the importance of pain management. The reluctance to adequately address pain reached an absurd degree when doctors withheld adequate pain relief for terminal cancer patients, or operated on newborns and children as old as 14 months (https://www.nytimes.com/1987/12/17/opinion/l-why-infant-surgery-without-anesthesia-went-unchallenged-832387.html) without anesthesia or analgesia. The rise of the hospice movement (https://en.wikipedia.org/wiki/Hospice#Rise_of_the_modern_hospice_movement) in the 1980's helped ease the suffering of the terminally ill, and around the same time specialists in pain management started promoting opiates for non-cancer pain. Russell Portenoy was a leading pain specialist at Memorial Sloan Kettering who in 1986 together with Kathleen Foley published a paper titled Chronic use of opioid analgesics in non-malignant pain; Report of 38 cases (https://www.sciencedirect.com/science/article/pii/0304395986900916#!) . Portenoy and Foley concluded "that opioid maintenance therapy can be a safe, salutary, and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse."

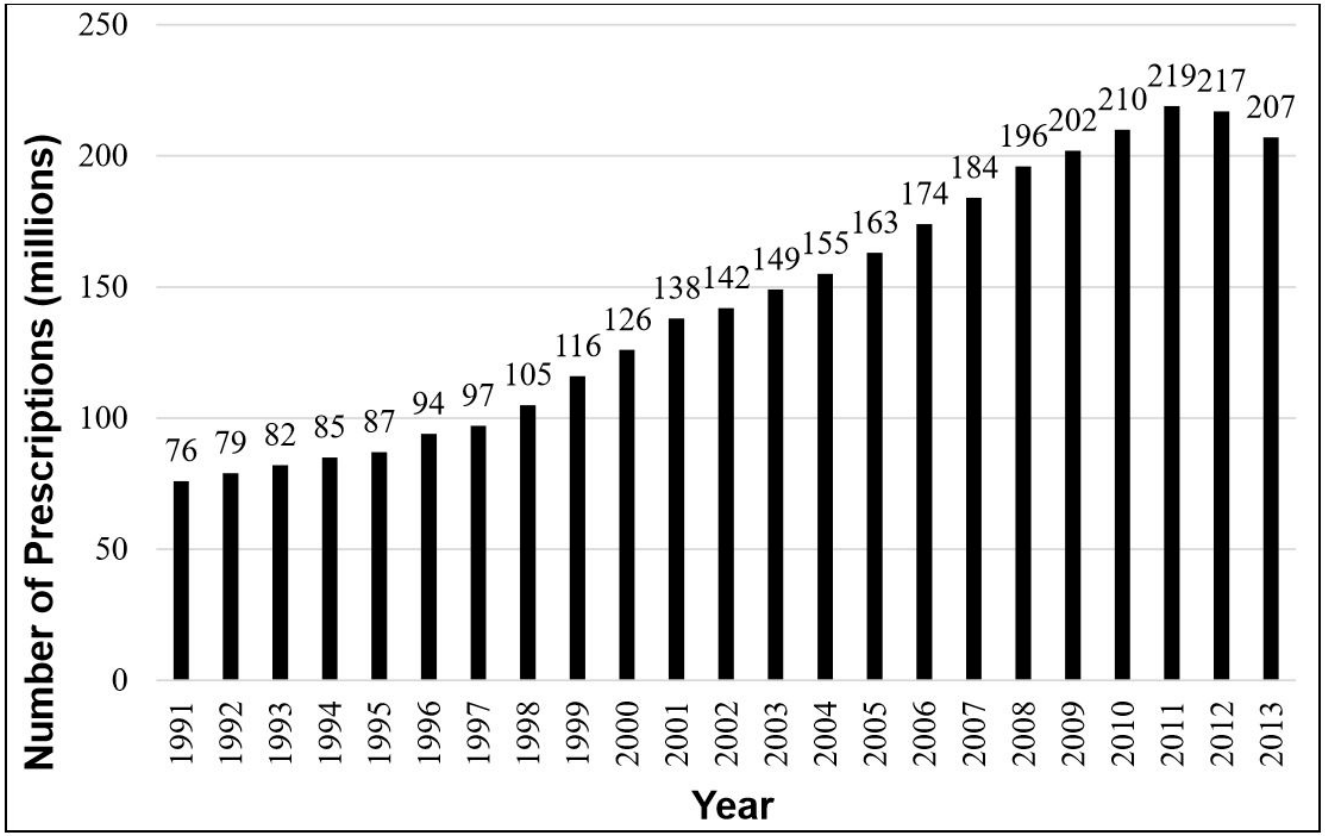
Another (small) data point was a letter to the New England Journal of Medicine (http://www.feinberg.northwestern.edu/sites/ipham/conferences/globalhealthsymposium/docs/PorterJickLetter.pdf) by Jane Porter and Hershel Jick from Boston University Medical Center. An analysis of the computerized medical records of 11,882 hospitalized patients who received at least one narcotic preparation only showed four patients who subsequently developed a narcotic addiction.

It was on the basis of these slim, almost anecdotal pieces of evidence that pain management doctors took up a crusade to prescribe opiates for non-malignant pain. As Brian Mandell writes (https://www.mdedge.com/ccjm/article/109138/drug-therapy/fifth-vital-sign-complex-story-politics-and-patient-care#) , *"In the mid-1990s, the American Pain Society aggressively pushed the concept of pain as the fifth vital sign. Their stated goals included raising awareness that patients with pain were undertreated, in large part because in the Society's opinion pain was not regularly assessed at physician office visits or even in the hospital after surgery. Half a decade later the Joint Commission and others hopped on this train, emphasizing that pain needs to be regularly assessed in all patients, that pain is a subjective measure, unlike the heart rate or blood pressure, and that physicians must accept and respect patient self-reporting of pain. Concurrent with these efforts was the enhanced promotion of pain medications."*

Hospitals were required to routinely assess patients' pain levels, and were concerned that they might lose accreditation if pain was under-treated. In 2001 a doctor lost a lawsuit (http://articles.latimes.com/2001/jun/15/news/mn-10726) charging him with elder abuse

for under-treating a lung cancer patient's pain. Between 1991 and 2010, the number of opiate prescriptions dispensed by retail pharmacies nearly tripled:

Figure 1. Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, 1991-2013.



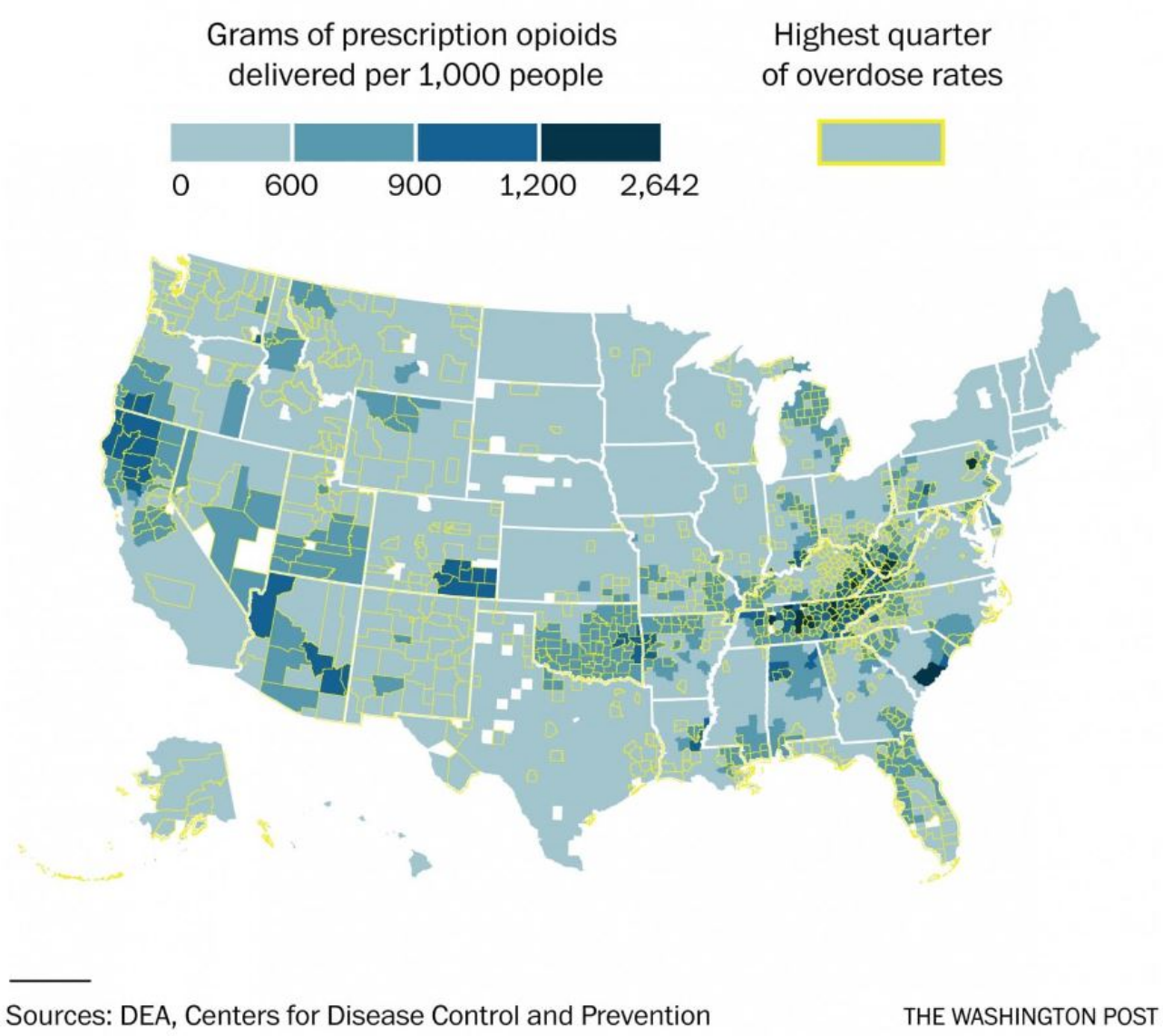
[INSERT OPIATE PRESCRIPTIONS DISPENSED BY US RETAIL PHARMACIES.JPG]

https://www.jointcommission.org/assets/1/6/Pain_Std_History_Web_Version_05122017.pdf **(https://www.jointcommission.org/assets/1/6/Pain_Std_History_Web_Version_05122017.pdf)**

The Purdue Sales Machine

Purdue Pharma launched Oxycontin in 1996 just as the medical establishment was receptive to prescribing more opioids. By 1998 Purdue had over 400 sales reps dedicated to selling Oxycontin. Sales grew from $48 million in 1996 to over $1 billion in 2000. The sales strategy was described by Dr. Art Van Zee in The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health

Tragedy (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/). The company used physician prescribing information from sister company IMS Health in order to target doctors who were already large prescribers of other opioids such as Percocet or Percodan. This allowed the sales force to go after existing pill mills: clinics run by unscrupulous doctors who sold prescriptions to addicts. The doctor targeting also took the sales force into rural America: places like Appalachia and Maine whose labor force of loggers or miners often had chronic pain injuries, and where globalization had led to high unemployment and lack of hope:



How drugs intended for patients ended up in the hands of illegal users (https://www.washingtonpost.com/investigations/how-drugs-intended-for-patients-ended-up-in-the-hands-of-illegal-users-no-one-was-doing-their-job/2016/10/22/10e79396-30a7-11e6-8ff7-7b6c1998b7a0_story.html?utm_term=.98ee961a7f46)

The Purdue sales force was trained to counter concerns about addiction. Relying on the Porter and Jick letter, the company's position was "If you take the medicine like it is prescribed, the risk of addiction when taking an opioid is one half of one percent." What Purdue was ignoring was the fact that if you took the medicine as it was prescribed, there was a good chance that you would become addicted and then would need to take higher doses. "A lot of these people say, 'Well, I was taking the medicine like my doctor told me to,' and then they start taking them more and more and more," Purdue senior medical director, Dr. J. David Haddox, told a reporter in 2001. "I don't see where that's my problem."

In 1999, a Purdue-funded study of patients who used OxyContin for headaches found that the addiction rate was thirteen per cent. As Van Zee said, *"Prescription drug abuse in a substantial minority of chronic-pain patients has been demonstrated in studies by Fishbain et al. (3%–18% of patients),*53 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib53) *Hoffman et al. (23%),*54 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib54) *Kouyanou et al. (12%),*55 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib55) *Chabal et al. (34%),*56 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib56) *Katz et al. (43%),*57 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib57) *Reid et al. (24%–31%),*58 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib58) *and Michna et al. (45%).*59 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/#bib59) *"*

The other key point that Purdue was ignoring was the fact that the time release coating on the pill could be defeated simply by letting the coating dissolve in your mouth for a few minutes. Then you were left with a 20, 40, 80 or 160 milligram pill of pure oxycodone which could be snorted or injected. Meier said that compared to a 5 milligram Percocet, OxyContin was a "nuclear bomb". Purdue used the FDA labeling *'Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug,'* to great effect, even though they knew that the coating could be removed by users. Indeed, MS Contin, with the same coating, had been widely targeted by addicts to the point that some pharmacies would not carry the drug for fear of theft. A Purdue marketing official, Mark Alfonso, had said in an email, *"I recall that I received this kind of news on MS Contin all the time, and from everywhere," Alfonso wrote. "Some pharmacies would not even stock MS Contin for fear they would be robbed. In Wisconsin, Minnesota and Oklahoma, we*

had physicians indicted for prescribing too much MS Contin." A 1990 scientific paper described this diversion: Recovery of morphine from a controlled-release preparation. A source of opioid abuse. **(https://www.ncbi.nlm.nih.gov/pubmed/2249204)**

In 2000 Art Van Zee, a rural doctor in Pennington Gap Virginia, was alarmed at the surge in OxyContin addiction in Appalachia and other parts of rural America. Van Zee contacted Purdue's spokesman Dr. David Haddox. Haddox had come to the attention of Purdue through his promotion of the theory of pseudoaddiction **(https://www.ncbi.nlm.nih.gov/pubmed/2710565)** : when a patient engages in opiate seeking behavior and dose escalation she is not addicted, she just needs more opiates. Van Zee urged Purdue to respond to the epidemic. He wrote, *"Larry and I appreciated meeting with David Haddox the other night. I appreciate very much David's time and interest in these issues of mutual concern. David had asked for some of my practical suggestions and I did give him a list written out on 11/20/00. Some of these may seem harsh and unrealistic. However, I don't think anyone ever would have imagined the scope and magnitude of abuse of OxyContin that is appearing in regions around the country. My fear is that these are sentinel areas, just as San Francisco and New York were in the early years of HIV [the virus that causes AIDS]. I don't think any of us understand all the reasons why this is occurring. Therefore, until this is better understood and come to terms with, I do suggest these measures to stop promoting OxyContin for use in chronic non-malignant pain. I would think, until things are better understood as to what is going on, that this would be in the best interest of public health and Purdue."*

One suggestion Van Zee had was to reformulate the pill to combine Oxycodone with Naloxone. The pill would still be effective if taken orally since stomach acid inactivates Naloxone, but if snorted or injected, the Naloxone would block the opiate receptors and prevent abuse. This approach had proven effective with another opiate, Talwin. Purdue's response to Van Zee was the same as their hard line approach to any criticism: "Any effort to restrict access to OxyContin would be a disservice to the thousands of patients who rely on this medication to control their pain and regain function of their lives," the company said. Van Zee also contacted the FDA with his concerns to no avail. In 2002 Van Zee traveled to Washington DC to testify in front of a Senate panel regarding the dangers of OxyContin abuse. Senator Chris Dodd of Connecticut, home state of Purdue Pharma, aggressively challenged Van Zee, using talking points given him by Purdue. Again, Van Zee's warnings went unheeded. But Chris Dodd was rewarded with $10,000 in campaign contributions from Purdue's political action committee, ten times more than the PAC gave to any other candidate that year.

Economics of OxyContin

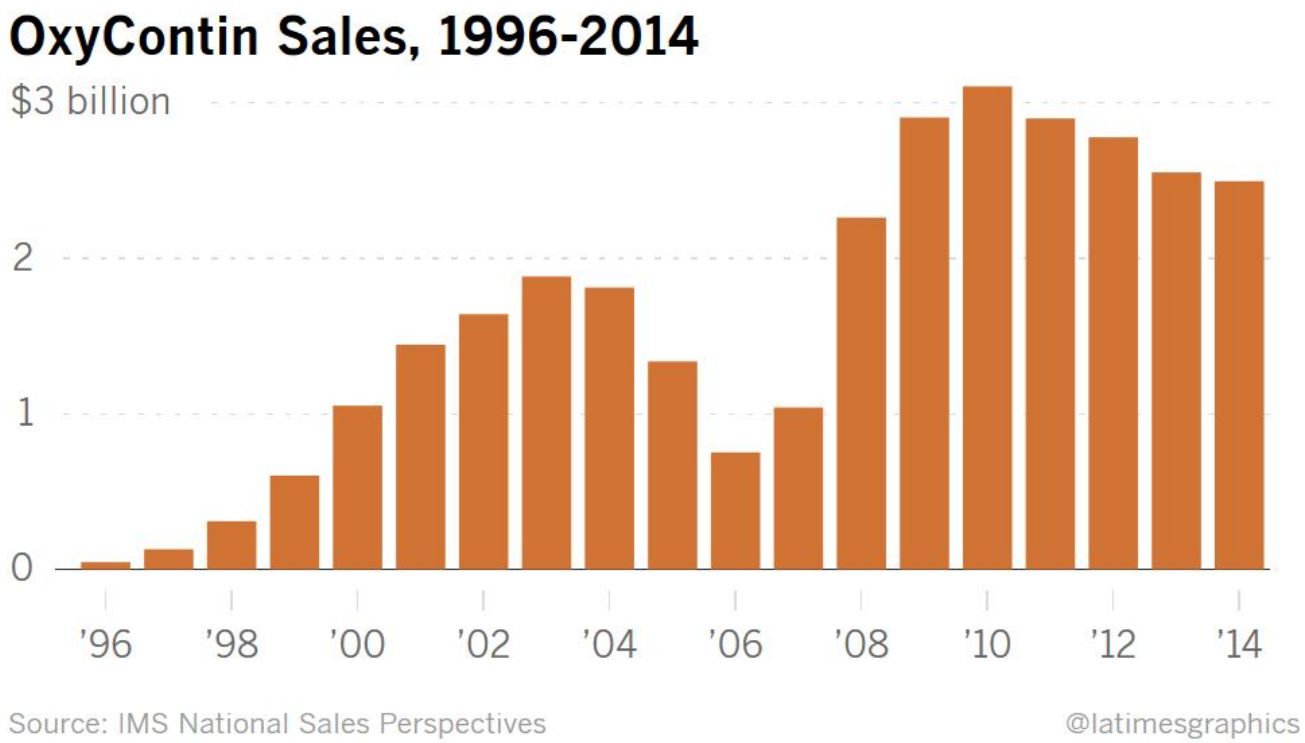
As a street drug, OxyContin sold for $1/milligram. A 40 milligram pill sold for $40, an 80 milligram pill for $80, etc. Yet Medicaid patients would pay only $3 for a bottle of one hundred 80 milligram tablets, worth $8,000 on the street (http://cicero.wustl.edu/Pubs/Inciardi-Goode%202003.pdf) . As Sam Quinones describes in Dreamland: The True Tale of America's Opiate Epidemic (https://www.amazon.com/Dreamland-True-Americas-Opiate-Epidemic-ebook/dp/B00U19DTS0/ref=sr_1_1?s=books&ie=UTF8&qid=1534621235&sr=1-1&keywords=dreamland) , this quickly led to rampant Medicaid fraud in depressed economic areas. Addicts would recruit their elderly friends, drive to a pill mill, and for a doctor's fee of $250, leave with a hundred pill supply. The addicts would sell the pills and split the money with their non-addict friends. Oxycontin became a license to print money. In fact, in Portsmouth, Ohio, OxyContin became an alternative currency, used to purchase cars, dentist services, toys, diapers, laundry detergent, and even drug free urine. Junkies would shoplift items to order in return for Oxy's, the price in milligrams of OxyContin being half of the sticker price of the item. A Walmart receipt, meanwhile, could get you cash. Junkies scoured Walmart parking lots for discarded receipts. They'd steal the items on a receipt, flashing the paper at the greeter as they left. Then they'd return the merchandise, with the receipt, and exchange it for cash.

The junkies didn't just steal from Walmart. They stole anything they could find of value from their friends and families: cash, guns, cars, appliances, tools, jewelry. They slipped into cancer patients' houses during the night and stole their pills. They stole copper wire, manhole covers, and Christmas presents. As had always happened in the past, many women took up prostitution to pay for their habit. *"Pill mills sprouted up all over, driven by locum tenens lists, a clearinghouse for doctors around the country seeking temporary employment, many of whom were desperate. Portsmouth for a while had a pill mill for every eighteen hundred residents. "My daughter was addicted," said Lisa Roberts, the city's public health nurse. "A judge's kid became addicted. A mayor's kid became addicted. A police chief's kid got addicted. The kids who came from excellent families got addicted." It seemed like an evil lottery, a massive brainwashing. One by one people succumbed. After a while, Roberts could recognize the look, say, in an old friend she hadn't seen for a while. "They're coming over to your house [with] these big elaborate stories to get money off you," she said. "It's like watching people being picked off one by one by one.'"*

Here is a poignant story about a young mother (https://www.nytimes.com/2018/07/20/opinion/sunday/opioid-addiction-treatment.html) suffering from opiate addiction.

It is unclear to me the percentage of pill addicts who became addicted iatrogenically (i.e. through a legitimate prescription) as opposed to those who started abusing pills recreationally. Perhaps you could have more sympathy towards the innocent chronic pain patient

who became addicted than the teenager who found leftover OxyContins in the medicine cabinet. Purdue Pharma would disclaim all responsibility for addictions resulting from recreational use, because the drug was not used as prescribed by a doctor. But the fact remains, those kids would not have become addicted without medicine cabinets across America having ample supply of leftover OxyContins which were prescribed for minor pain.



http://www.latimes.com/projects/oxycontin-part1/ **(http://www.latimes.com/projects/oxycontin-part1/)**

In the early 2000's, Purdue Pharma was going gangbusters. By 2003 sales were approaching $2 billion and nearly half the prescribers were general practitioners. However the company was coming under increasing criticism due to press reports of the opiate epidemic in the midwest. The corporate response was to stonewall any criticism and back up their statements with scientific studies. One such study published in 2000 was conducted by David Joranson's Pain and Policies Studies Group at the University of Wisconsin. Titled Trends in medical use and abuse of opioid analgesics **(https://www.ncbi.nlm.nih.gov/pubmed/10755497)**, the study looked at prescribing rates and emergency room visits and concluded "The trend of increasing medical use of opioid analgesics to treat pain

does not appear to contribute to increases in the health consequences of opioid analgesic abuse." "This study suggests that increased use of opioid pain medications resulting in abuse may be based more on myth than reality," one of Joranson's co-authors wrote. However, the data for the study had been collected from 1990 to 1996, prior to the introduction of OxyContin. By 1998, the emergency room visits for OxyContin started to soar. As it happened, Purdue Pharma was one of the largest contributors to Joranson's Pain and Policies Studies Group, highlighting the potential corrupting nature of research funding.

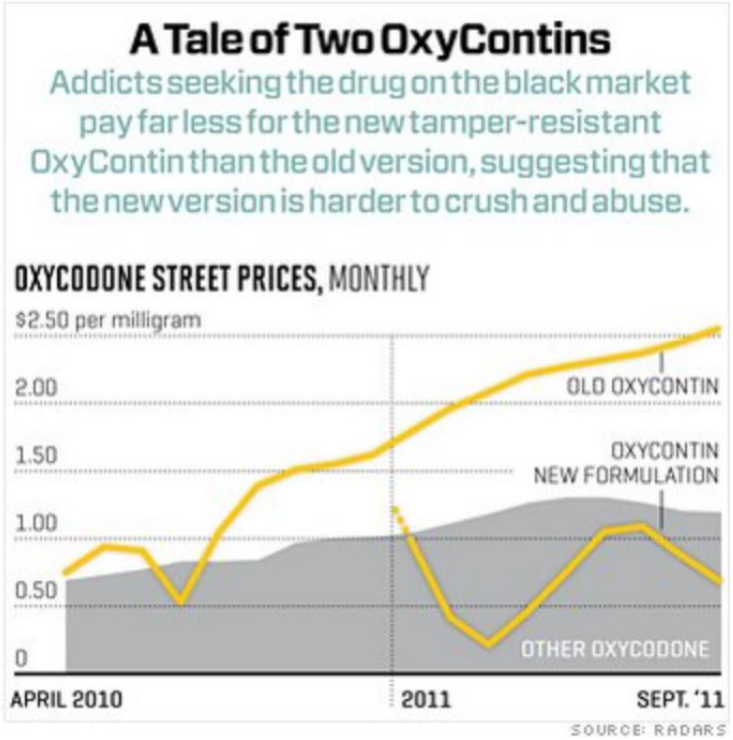
Hundreds of lawsuits against Purdue Pharma, later to become thousands, started pouring in the early 2000's. Purdue got suits dismissed by asserting, among other defenses, a legal doctrine which shields drug companies from liability when their products are prescribed by trained physicians. Purdue settled other lawsuits on confidential terms. One class action lawsuit was settled for $75 million. These were minor costs of doing business when revenues exceeded $1 billion.

In 2006 Federal prosecutors prepared a case against Purdue alleging the company had acted criminally by training its sales representatives to misrepresent OxyContin's potential for abuse and addiction. According to Fortune magazine **(http://fortune.com/2011/11/09/oxycontin-purdue-pharmas-painful-medicine/)** , *"The case grew so serious, Fortune has learned, that federal prosecutors formally recommended charging Purdue and its three top executives (but none of the Sacklers) with multiple felonies including conspiracy, mail and wire fraud, and money laundering, in addition to misbranding. But Purdue dodged the worst charges. The company hired an all-star defense team, including Mary Jo White, a former U.S. attorney, and Rudolph Giuliani, then the Republican Party's presumptive presidential front-runner. The company was able to appeal above the heads of the prosecutors on the case and met with the head of the Justice Department's criminal division.*
Eventually the two sides agreed that Purdue would plead guilty to a single felony count of misbranding. In May 2007 the company agreed to pay a $600.5 million fine, and its top three executives were fined $34.5 million (though the company picked up the tab) and subsequently left Purdue."

According to Barry Meier, a key issue in the case was when senior corporate executives learned about Oxycontin's potential for abuse. *"If regulators at the FDA or lawmakers had learned early on about the drug's abuse, then Purdue risked losing its unique labeling claim—the one celebrated by company officials as its "principal selling tool"—just as the massive marketing campaign for OxyContin was starting."* Meier reveals, in part from sealed records in the federal lawsuit that were leaked to him, that management knew about OxyContin's likelihood of abuse from as early as 1997, and thus should have notified the FDA and should not have marketed the drug as unlikely to be abused. Yet that evidence was buried. Even a $635 million fine was a slap on the wrist for such a popular drug. After the drama of the federal lawsuit died down sales shot up to $3 billion per year by 2010.

Reformulation

In 2010 Purdue Pharma finally released a reformulated version of OxyContin designed to reduce abuse. Instead of just a thin time release coating around a bolus of pure oxycodone, the new pill was a thick gum, impossible to snort and difficult to dissolve and inject. The reformulation worked. The street value of the old formulation soared and the street value of the new formulation plummeted:



http://fortune.com/2011/11/09/oxycontin-purdue-pharmas-painful-medicine/ **(http://fortune.com/2011/11/09/oxycontin-purdue-pharmas-painful-medicine/)**

Drug addicts told law enforcement that all the OxyContin addicts that they knew switched to heroin. However, with OxyContin, the addicts knew the exact dosage they were taking. With heroin, the dosage was unknown, which raised the risk of overdose. This paper **(https://www3.nd.edu/~elieber/research/ELP.pdf)** argues that the rapid rise in heroin death rates (see graph at top of page) is largely due to the reformulation of OxyContin in 2010. We'll take an in depth look at the heroin and fentanyl epidemic in the next session.

Support from the American Medical Association

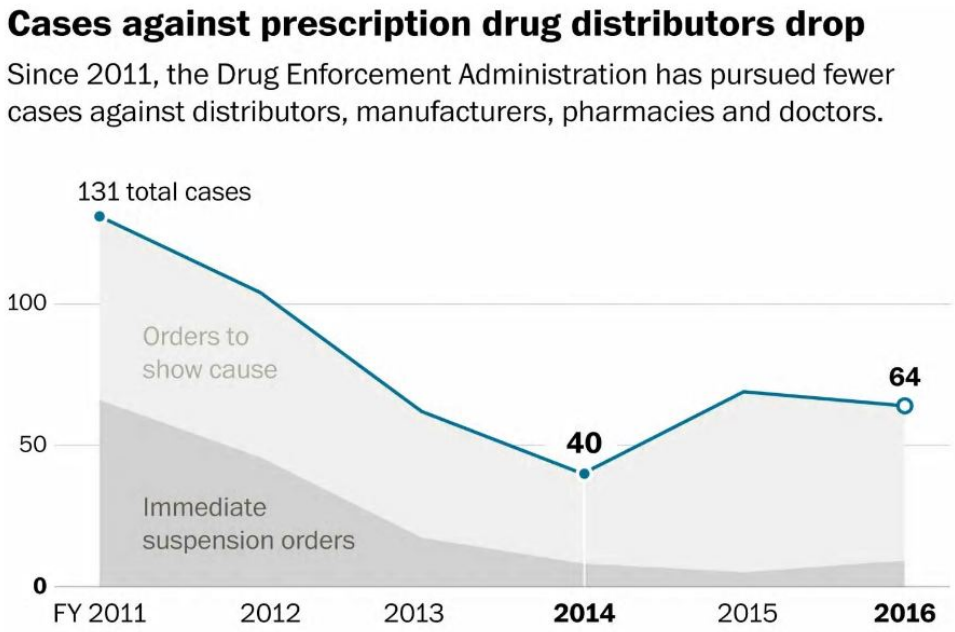
As the crisis worsened a variety of ideas were explored that might help to stop the epidemic. One idea was prescription monitoring. Many addicts practiced doctor shopping: getting many opiate prescriptions from many doctors for the same real or pretend ailment. A centralized prescription registry would help to flag this practice. According to Meier, drug companies, the American Medical Association and pain specialists argued that prescription monitoring would have a "chilling effect" on legitimate prescribing, because doctors feared landing on law enforcement's radar. David Joranson of the Pain and Policy Studies Group wrote, "Requiring the use of these prescription forms would send an unmistakable message to physicians that prescribing controlled substances could give them an unwanted high profile with the police or licensing authorities if they order more than a minimal amount for patients in pain." States finally began implementing prescription drug monitoring programs starting around 2010 and as of today 37 states have them. They seem to have been effective **(https://www.cdc.gov/drugoverdose/policy/successes.html)** in reducing the amount of opiates prescribed, although the results may be confounded by the reformulation of OxyContin and the switch to black market heroin around the same time frames.

Another suggestion for reducing the scope of the opioid crisis was physician training. Opiates were now being prescribed by tens of thousands of general practice doctors without specific knowledge or training in addiction or opiate pharmacology. In order to prescribe methadone or Suboxone, two opiates used in recovery, doctors needed to complete eight hours of specialized training. Shouldn't doctors who prescribe more addicting drugs like OxyContin be required to have training? This proposal was floated by the FDA but the American Medical Association bitterly opposed it as inconvenient for doctors. A decade later, as the opiate crisis intensified the Obama administration revisited the physician training proposal. Again the American Medical Association made it clear to administration officials that they would go to war over such a proposal, and the White House backed down.

Congress to the Rescue!

The DEA had another tool to slow the epidemic of prescription opiates. Under Nixon's 1970 Comprehensive Drug Abuse Prevention and Control Act, drug distributors were required to monitor their customers for signs that legal drugs were being diverted. Using this law the diversion of up to half of pharmaceutical grade amphetamines and barbiturates was halted in the 1970's. In 2004 the DEA recognized that the problem of pharmaceutical opiates was eclipsing the problem of heroin and cocaine, and they started to threaten drug distributors with enforcement actions unless they stopped shipping to obvious pill mills and pharmacies with excessive opiate prescriptions. As outlined in **this Washington Post article (https://canvas.harvard.edu/courses/41939/files/6268984/download?wrap=1)**

(https://canvas.harvard.edu/courses/41939/files/6268984/download?wrap=1) , initial efforts in 2006 and 2007 were successful, shutting down small distributors and settling cases against two out of the top three drug distributors: McKesson, AmerisourceBergen and Cardinal Health, which together account for 85 percent of the drug shipments in the United States. In 2009 Congress passed a law shutting down internet pharmacies which distributed controlled substances, and required doctors to see their patients face to face before writing prescriptions. However, starting in 2011, senior officials in the Justice Department started to intercede in the DEA diversion cases, slowing or halting ongoing investigations:



https://www.washingtonpost.com/investigations/the-dea-slowed-enforcement-while-the-opioid-epidemic-grew-out-of-control/2016/10/22/aea2bf8e-7f71-11e6-8d13-d7c704ef9fd9_story.html?utm_term=.74274cf51c77 **(https://www.washingtonpost.com/investigations/the-dea-slowed-enforcement-while-the-opioid-epidemic-grew-out-of-control/2016/10/22/aea2bf8e-7f71-11e6-8d13-d7c704ef9fd9_story.html?utm_term=.74274cf51c77)**

This slowdown was happening at the height of the crisis at a time when huge amounts of legal opiates were being diverted to illegal use. As Meier reports, *"Between 2007 and 2012, the three biggest wholesalers of prescription drugs in the United States—McKesson, Cardinal, and AmerisourceBergen—shipped 780,000,000 pain pills containing oxycodone or hydrocodone to West Virginia, a state*

already rife with opioid addiction, a newspaper there reported. The volume represented a quantity large enough to supply every man, woman, and child in the state of West Virginia with 433 pills."

Part of the reason for Justice interceding in DEA affairs may have been old fashioned lobbying. According to this report **(https://www.publicintegrity.org/2016/09/18/20203/pharma-lobbying-held-deep-influence-over-opioids-policies)** , between 2006 and 2015, Purdue and other painkiller producers, along with their associated nonprofits, spent nearly nine hundred million dollars on lobbying and political contributions—eight times what the gun lobby spent during that period.

Another reason for the intervention may have been a strategy by the major drug distributors and their law firms to hire away DEA people involved in preventing diversion. Since 2005 thirty-one DEA officials have been hired away **(https://www.washingtonpost.com/investigations/key-officials-switch-sides-from-dea-to-pharmaceutical-industry/2016/12/22/55d2e938-c07b-11e6-b527-949c5893595e_story.html?utm_term=.6ded30adc4d7)** from the diversion division.

Finally, in 2016 Congress stepped in to resolve the issue. Under the Ensuring Patient Access and Effective Drug Enforcement Act, sponsored by Reps. Tom Marino (R-Pa.) and Marsha Blackburn (R-Tenn.), Congress removed the DEA's ability to obtain an immediate suspension order against a drug distributor who was shipping drugs that were being diverted to illegal use **(https://www.washingtonpost.com/graphics/2017/investigations/dea-drug-industry-congress/?utm_term=.74d909d85c75)** . Tom Marino was rewarded by being nominated by President Trump to be the nation's drug czar, but the resultant furor caused him to withdraw his nomination **(http://www.toledoblade.com/Politics/2017/10/17/Trump-Drug-czar-nominee-Tom-Marino-withdrawing-his-name/stories/feed/index.rss)** .

And Now For Some Good News

Raymond and Beverly Sackler (credit: Taco van der Eb/Hollandse Hoogte/Redux).

https://www.forbes.com/sites/alexmorrell/2015/07/01/the-oxycontin-clan-the-14-billion-newcomer-to-forbes-2015-list-of-richest-u-s-families/#153e13b875e0 **(https://www.forbes.com/sites/alexmorrell/2015/07/01/the-oxycontin-clan-the-14-billion-newcomer-to-forbes-2015-list-of-richest-u-s-families/#153e13b875e0)**

In 2015, the Sackler family was added to Forbes list of richest American families. With an estimated net worth of $14 billion, the Sacklers built the 16th largest American fortune, greater than the Rockefellers or the Mellons. Congratulations Sacklers!

The Pendulum Swings Back: From Opiophilia to Opiophobia

Since the recommendations to use opiates for long term chronic pain conditions were based on scant evidence, researchers finally started to examine the issue. A 2003 paper in the New England Journal of Medicine concluded that long term opiate therapy for chronic pain may be neither safe nor effective (http://psycnet.apa.org/record/2003-09949-004). Pain management doctors now advocate multiple approaches for chronic pain including physical therapy, cognitive behavioral therapy, transcutaneous nerve stimulation, and non-opiate pain relievers such as pregabalin. In 2016 the Centers for Disease Control published guidelines for prescribing opiates for chronic pain (https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm); the guidelines urged caution when prescribing opioids, warned against dosages as high as 90 morphine milligram equivalents, and suggested continued regular monitoring and switching from opiates to other therapies when indicated. Many states are adopting the CDC guidelines and physicians are under pressure to conform to the new opiophobia environment. This is having terrible consequences for tens of thousands of long term chronic pain patients who have been addicted by their doctors and are taking daily doses of up to 600 milligrams, who are now contemplating suicide (https://www.kitsapsun.com/story/news/2018/07/26/chronic-pain-patients-feel-sting-drug-opioid-crackdown/822848002/). This **Washington Post article** (https://canvas.harvard.edu/courses/41939/files/6268991/download?wrap=1) (https://canvas.harvard.edu/courses/41939/files/6268991/download?wrap=1) tells their story.

Another problem is that hospitals across America have extreme shortages of injectable opiate drugs (http://www.htvnativeadsolutions.com/wcvb/sponsoredarticles/adv/?prx_t=na8DAHRQhAR9QMA). The DEA limits the amount of opiate materials any one drug maker can use and the drug makers have been allocating the materials to high margin pills rather than low margin injectable solutions. It's a world awash in opiates, just not in the hospitals where they're needed.

Preparation

Please read the text above and click through the hyperlinks and read whichever of them look interesting. Please email me with any questions or topics that you would like to discuss in class. Please send the email no later than the day before class, to **ocurme@gmail.com** (mailto:ocurme@gmail.com).

Additional Resources

List resources