AMERICA'S OPIOID EPIDEMIC

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The Opioid Problem

Opioid abuse in the United States is reported to be at an all-time high. The Centers for Disease Control and Prevention (CDC) recently estimated that the total "economic burden" of prescription opioid misuse alone in the United States is $78.5 billion a year, including the costs of health care, lost productivity, addiction treatment, and criminal justice involvement.[1] In 2015, over 33,000 Americans died as a result of an opioid overdose.[2] The exceptional costs in monetary value and life has garnered attention from both the public and private sector as leaders search for mechanisms to help decrease the impact of the epidemic.

The opioid crisis began in the mid-to-late 1990's following a confluence of events that led to a dramatic increase in opioid prescribing, including: a regulatory, policy and practice focus on opioid medications as the primary treatment for all types of pain;[3] an unfounded concept that opioids prescribed for pain would not lead to addiction; [4] the release of guidelines from the American Pain Society in 1996 encouraging providers to assess pain as "the 5th vital sign" at each clinical encounter; and the initiation of aggressive marketing campaigns by pharmaceutical companies promoting the notion that opioids do not pose significant risk for misuse or addiction and promoting their use as "first-line" treatments for chronic pain.[5]

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[1] Florence, C. S., Zhou, C., Luo, F. & Xu, L. (2016) The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Medical Care* **54**, 901-906, doi:10.1097/MLR.0000000000000625

[2] Rudd, R. A., Seth, P., David, F. & Scholl, L. (2016) Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. *MMWR Morb. Mortal. Wkly. Rep.* **65**, 1445-1452, doi:10.15585/mmwr.mm655051e1

[3] Rosenblum, A., Marsch, L. A., Joseph, H. & Portenoy, R. K. (2008) Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions. *Experimental and clinical psychopharmacology* **16**, 405-416, doi:10.1037/a0013628

[4] Van Zee, A. (2009) The promotion and marketing of OxyContin: commercial triumph, public health tragedy. *Am J Public Health* **99**, 221-227, doi:10.2105/AJPH.2007.131714

[5] Van Zee, A. (2009) The promotion and marketing of OxyContin: commercial triumph, public health tragedy. *Am J Public Health* **99**, 221-227, doi:10.2105/AJPH.2007.131714

Cicero, T. J., Inciardi, J. A. & Munoz, A. (2005) Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004. *J Pain* **6**, 662-672, doi:10.1016/j.jpain.2005.05.004

Morone, N. E. & Weiner, D. K. (2013) Pain as the fifth vital sign: exposing the vital need for pain education. *Clin Ther* **35**, 1728-1732, doi:10.1016/j.clinthera.2013.10.001

Centers for Disease, C. & Prevention. (31013) Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb. Mortal. Wkly. Rep.* **60**, 1487-1492

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Prescription opioids, heroin, and synthetic opioid drugs all work through the same mechanism of action. Opioids reduce the perception of pain by binding to opioid receptors, which are found on cells in the brain and in other organs in the body. The binding of these drugs to opioid receptors in reward regions in the brain produces a sense of well-being, while stimulation of opioid receptors in deeper brain regions results in drowsiness and respiratory depression, which can lead to overdose deaths. The presence of opioid receptors in other tissues can lead to side effects such as constipation and cardiac arrhythmias through the same mechanisms that support the use of opioid medications to treat diarrhea and to reduce blood pressure after a heart attack. The effects of opioids typically are mediated by specific subtypes of opioid receptors (mu, delta, and kappa) that are activated by the body's own (endogenous) opioid chemicals (endorphins, encephalin). With repeated administration of opioid drugs (prescription or illicit), the production of endogenous opioids decreases, which accounts in part for the discomfort that ensues when the drugs are discontinued (*i.e.*, withdrawal).[6] The inaccurate guidelines promoting the prescription of opioids in conjunction with their addictive nature portended the upcoming crisis.

The sale of prescription opioids more than tripled between 1999 and 2011, and this was paralleled by a more than four-fold increase in treatment admissions for opioid abuse and a nearly four-fold increase in overdose deaths related to prescription opioids.[7] Federal and state efforts to curb opioid prescribing resulted in a leveling off of prescriptions starting in 2012;[8] however, heroin-related overdose deaths had already begun to rise in 2007 and sharply increased from just over 3,000 in 2010 to nearly 13,000 in 2015. [9] Researchers now know prescription opioid misuse is a significant risk factor for heroin use; 80 percent of heroin users first misuse prescription opioids. While only about four percent of people who misuse prescription opioids initiate heroin use

[6] Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S. & Parker, K. L. (2006) *Goodman & Gilman's the pharmacological basis of therapeutics*. 11th edn, (McGraw-Hill)

[7] Centers for Disease, C. & Prevention. (2013) Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb. Mortal. Wkly. Rep.* **60**, 1487-1492

[8] Dart, R. C. *et al.* (2015) Trends in opioid analgesic abuse and mortality in the United States. *N. Engl. J. Med.* **372**, 241-248, doi:10.1056/NEJMsa1406143

[9] Rudd, R. A., Seth, P., David, F. & Scholl, L. (2016) Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. *MMWR Morb. Mortal. Wkly. Rep.* **65**, 1445-1452, doi:10.15585/mmwr.mm655051e1

within 5 years, for this subset of people the use of the cheaper, often easier to obtain street opioid is part of the progression of an opioid addiction. [10]

The root cause of the opioid epidemic is difficult to discern. Non-medical personnel are the primary abusers of opioids. However, opioids are a controlled narcotic and require a prescription to procure. America is approximately 5% of the world's population but consume 75% of the world's prescription medications. [11] This disproportionate administration and subsequent use of prescription drugs in the U.S. places culpability on all parties – doctors, patients, and aggressive pharma corporations. Additionally, 20% of the non-cancer patients with symptomatic pain receive an opioid prescription. [12]

As previously mentioned, the medical community underestimated the addictive nature of opioids and overprescribed them. Currently, the medical community now concurs on the research highlighting the dangerous nature of long term opiate use. Another problem, however, is the difficulty medical professionals have in assessing patient pain, monitoring use across a large patient population, and determining the proper time to stop prescribing opioids. A New York Times article researched the prescription of opioids and found that 18% of all prescriptions for opioid analgesics were written by family practitioners, and 15% by internists, compared to 5% for pain specialists.[13] Even though the consensus around opioids is the drugs are dangerous and should be used with caution, accurately diagnosing a patient's pain is difficult, and many doctors still turn to opioids to address short and long-term patient pain.

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[10] Muhuri, P. K., Gfroerer, J. C. & Davies, M. C. (2013) (CBHSQ [Center for Behavioral Health Statistics and Quality] Data Review)
Carlson, R. G., Nahhas, R. W., Martins, S. S. & Daniulaityte, R. (2013) Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug Alcohol Depend* **160**, 127-134, doi:10.1016/j.drugalcdep.2015.12.026
Compton, W. M., Jones, C. M. & Baldwin, G. T. (2016) Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med* **374**, 1296, doi:10.1056/NEJMc1601875
[11] Matt Berry. Are Doctors to Blame for Prescription drug abuse (April 2015) http://www.rehabs.com/are-doctors-to-blame-for-prescription-drug-abuse/
[12] CDC Guidelines for Prescribing Prescription Opioid for Chronic Pain – United States (2016) https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
[13] Richard Friedman, How Doctors Helped Drive the Addiction Crisis (November 2015) https://www.nytimes.com/2015/11/08/opinion/sunday/how-doctors-helped-drive-the-addiction-crisis.html?_r=0

When reviewing the literature on the opioid problem, pharmaceutical manufactures take a fair share of the blame. As pointed out in the 2016 article[14] in the Observer by Dr. Ronald Hirsch, it was big pharma who issued the original studies that prompted the faulty guidelines issued in the mid-to-late 1990s during the genesis of the crisis. The pharmaceutical manufacturer at the epicenter of this theory is Purdue Pharma, the maker of OxyContin. In 2007 Purdue Pharma pleaded guilty, as a corporation, to a felony related to the false marketing of OxyContin, and paid a fine of $635 Million. Three top executives also plead guilty and paid fines. [15] This example highlights nefarious actions by big pharma to promote an addictive treatment for patients; providing physicians with an alternative narrative placing blame on pharma and the corresponding guidelines and marketing issued based on studies of questionable veracity.

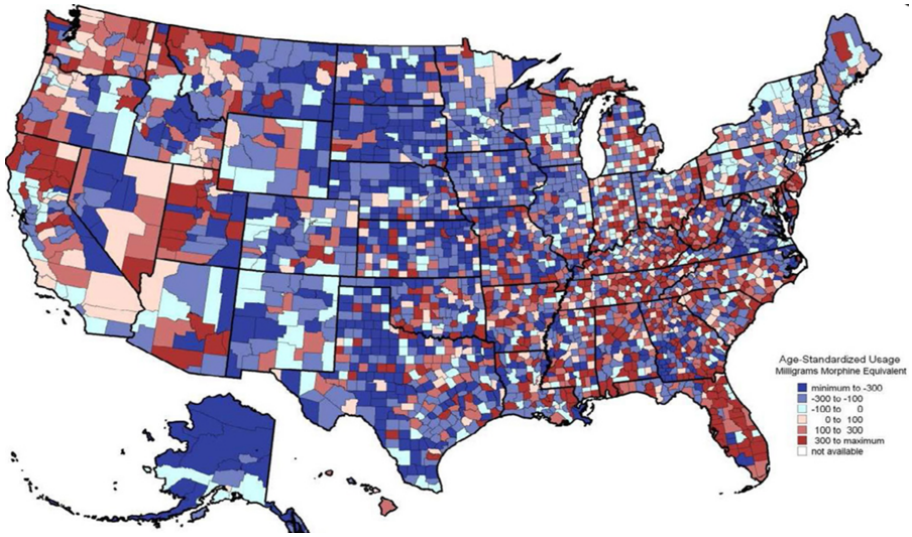
Patients are the final component of the prescription drug ecosystem, and the most difficult to assess. Certainly, adults who become addicted to opioids and end up misusing the narcotic should bear some of the responsibility for the epidemic. However, most research focuses on identifying the demographics associated with abuse rather than placing blame. These demographics are[16]:

- Rates of long-standing opioid medication use without a prescription are highest among younger users between the ages of 18 and 25, yet overdose rates are highest among users between 45 and 54 years old. The biggest increase in non-medical use of prescription pain relievers occurred in users 50 years and older—average rates of use in this group increased by 60% between 2003 and 2010.
- Rates of opioid prescriptions have been found to be highest among white patients, followed by black patients, Hispanic patients, and Asian or other race patients, regardless of socio-economic status.
- People from high Social Economic Status (SES) areas suffering from moderate-to-severe pain are prescribed more opioid medications than those in the low SES neighborhoods.

[14] Ronald Hirsch, The Opioid Epidemic: It's Time to Place Where It Belongs (May 16) http://observer.com/2016/05/the-opioid-epidemic-its-time-to-place-blame-where-it-belongs/
[15] Charles Lan, Who is to Blame for the Opioid Epidemic (March 2017) https://www.washingtonpost.com/opinions/who-is-to-blame-for-the-opioid-epidemic/2017/03/29/834c0024-14be-11e7-833c-503e1f6394c9_story.html?utm_term=.89c484d3efc3
[16] Lauren Brande, Prescription Opioid Addiction: What is Causing the Epidemic, http://drugabuse.com/library/prescription-opioid-addiction/

Education has also been associated with rates of opioid prescriptions. Patients with higher education levels are three times less likely to receive an opioid medication prescription than those with lower education levels

- In the United States, abuse rates are highest in the Southeastern states, Appalachian area, and Northwest. Rural regions also tend to have higher rates of prescription opioid overdose than urban areas.



Opioid Treatment

Approximately 3 million Americans and 16 million people across the world suffer from opioid addiction. [17] The primary treatments for opioid addiction are either medically supervised withdrawal or prescription treatment. Medically supervised withdrawal occurs when an opioid addict stops taking opioids and a doctor or treatment facility monitors the addict to ensure safe withdrawal and provides medical treatment as necessary. However, by itself, medically supervised withdrawal is usually not sufficient to produce long-term recovery, and it may increase the risk of overdose among patients who have lost their tolerance to opioids (i.e., the need for higher doses of the drug to produce effects) and resume the use of these drugs. [18] Therefore, the treatment of opioids with other medications is typically used. The most effective approach to treating a patient who has withdrawal is to prescribe a long-acting oral opioid (usually methadone or buprenorphine [Buprenex]) to relieve

[17] Soyka M. (2015) New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone. *Substance Abuse Rehabilitation;*6:1-14

[18] Hser YI, Saxon AJ, Huang D, et al. (2014) Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction;*109:79-87
Evans E, Li L, Min J, et al. (2015) Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. *Addiction;*110:996-1005

symptoms and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid. However, only licensed addiction-treatment programs (both office-based treatments and inpatient treatments) and physicians who have completed specific training regarding opioid drugs can administer opioids to treat opioid-use disorders. [19]

The cost of opioid treatment varies with the length of stay, exclusivity of treatment facility, and reputation of facility. Furthermore, the percentage of treatment covered by insurers also varies widely. The following guidelines for cost can be found on the website: www.addictioncenter.com.

- Outpatient Detoxification: $1,000 – $1,500
- Inpatient Rehab: $12,000 – $60,000 for 3 months
- Outpatient Rehab: $5,000 – 10,000 for 3 months
- Medications: Average of $4,700 a year.

Opioid Epidemic Solutions

Even though clinicians, patients, and pharmaceutical companies all have an integral role in the nation's epidemic, many solutions focus on the middleman – clinicians. Clinicians are the gatekeepers; have the ability to refute pharmaceutical studies and deny their organizations partnerships with certain manufacturers. Additionally, clinicians, unlike pharmaceutical representatives, interact with patients regularly and are in a better position to administer or deny opioids. For this reason, the CDC issued new guidance in 2016 specifically designed to assist clinicians in the prescription of opioids.

The CDC guidance focused on three areas: determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; assessing risk and addressing harms of opioid use. Highlights from the guidance are: the use of exercise/physical therapy in lieu of medication, minimal use of extended release opioids, clearly defined and articulated treatment goals, prescription of lowest dosage and systematic increases, more frequent treatment reevaluation, better assessment of patient risk factors, and drug testing to identify addicts.

[19] Sullivan LE, Fiellin DA. (2008) Narrative review: buprenorphine for opioid-dependent patients in office practice. *Annals Intern Med;*148:662-670

These guidelines, as well as a host of other solutions that can be found on the CDC's website, put the fate of the opioid epidemic in the hands of clinicians. The problem is that clinicians are already busy, sometimes undertrained in the prescription of opioids, and have difficulty tracking the numerous guidelines across a wide patient base. This problem creates an opportunity for the private sector to provide clinicians with the tools they need to adhere to industry best practices.

Opioid Market

Estimating the size of the opioid-solution market is difficult. One measure could be the cost of $78.5 billion that CDC quotes; if companies reduce that cost, then they would be providing a service many clinicians, health systems, employers, and municipalities need. The second measure would be to look at the opioid market in the U.S., which is valued at $12.4 billion,[20] and make a calculation based on administration fees. For example, if clinicians prescribe $12.4 billion in opioid medications, a company could charge a 1% fee for assisting in the management of opioids; The market under this scenario of long term opioid management can be estimated at $124,000,000 annually. The final method that could be used to estimate the market is a treatment based estimate. As stated, approximately 3 million Americans at any given time are suffering from opioid addiction. Using the treatment costs above from the addiction center, highlights from the article that successful treatment usually entails both treatment and alternate medication, in conjunction with socioeconomic trends indicating that opioid misuse is highest in rural areas and amongst youth, an estimated cost of treatment is $4,700 a year for medication and $9,750 for a 3-month treatment (average low end inpatient and mean outpatient costs – indicative of lower economic and young patients) or $14,450 per patient annual treatment cost. This figure would yield a market estimate of $43 billion to treat 3 million addicts annually.

Opioid solutions can vary from assisting clinicians with management of prescriptions to providing innovative treatment options for patients of variable economic status. Where a company chooses to focus, will determine the market size for that company, affect barriers to entry, and lead to different levels of competition.

[20] Grandview Research, Industry Insights (August 2016) http://www.grandviewresearch.com/industry-analysis/north-america-opioid-market

Snapshot of Opioid Startup Landscape

Company	Solution	Funding	Location
Kineta	Biotech company uses sea snail venom as alternative to opioids.	20M/11 rounds 1.5M Venture	Seattle, WA
180 Health Partners	Counseling based organization working with pregnant mothers to reduce prenatal addiction.	3M/ 1 round/ Venture	Franklin, TN
Axial Healthcare	Software prescription management tool	26M/4 rounds/7 Investors	Nashville, TN
Sollis Therapeutix	Pharmaceutical based solution	Pre-funding	Columbus, OH
RX Assurance: OpiSafe	Software prescription management tool	760k/1 round	Denver, CO
Biobot labs	Municipal management tool that allows governments to analyze sewage to identify addicted population clusters.	Pre-funding. Won MIT's DesignX Accelerator	Boston, MA
Blue Therapeutics	Developing non-opioid based pain killer	No Funding/Pre-Clinical Trials	Boston, MA
Groups. Recover Together	Specialized opioid treatment facilities	10M+/Venture	New York, NY
SelfRefind	Substance abuse treatment facilities	2-3M/Angel	Kentucky/Ohio
Affirm Health	Software prescription management tool	150k/ 1 round/seed	Nashville, TN

Funding data - Crunchbase

The above snapshot of the start-up landscape addressing the opioid epidemic shows that most Startups are focusing on either an alternate non-opioid medication for pain or a software management tool for assisting in the administration of opioids. What is noticeable absent from the search of the opioid Startup landscape are companies trying to innovate around the concept of addiction treatment.

There are companies such as WeConnect that aim to provide a digital support community for recovering alcoholics and addicts. Additionally, companies such as Ginger.io are using technology to facilitate more frequent interaction between patients and therapist. Both products, like similar products in this space, are aimed at broad addiction or counseling in general and not specifically opioid treatment.

The biotech approach to solving the opioid epidemic is the most straightforward and will yield the highest profitability. A biotech company that can create an alternate form of pain medication that doesn't use opiates in its base formula would be easy to commercialize. Another approach is to develop pharmaceuticals that address the opioid addiction. For example, Braeburn Pharmaceuticals developed an implant, Probuphine, used to treat certain adults who are addicted to opioids. Using biotechnology to address opioid addiction at a lower cost with better outcomes would also be highly profitable.

The last approach is the development of management software to assist physicians administering opioids. As previously stated, some physicians lack the training, expertise, and monitoring mechanisms to safely prescribe opioids to patients for long term chronic pain. The difficulty in this approach is aligning cost savings with the user. Physicians and provider organizations lack the incentive to purchase software that facilitates better opioid management because poor prescription management does not cost health care providers more money. However, companies could leverage payers to pressure providers to use software that yields better prescription management since payers incur the cost of opioid prescriptions and addiction treatment.

The opioid epidemic offers three clear entry points for startups. A biotech enabled solution will yield the most profit and has a clear path to commercialization. A patient or addict centered solution may gain user traction but has an unclear path to profitability. The clinician centered solutions are gaining modest traction; however, the value creation model is difficult to ascertain. Clinicians would benefit from software based tools, but the patients and payers absorb the costs associated with addiction. Therefore, a startup trying to enter this space would have to develop a product that provides benefits for both providers and payers to gain significant market penetration.