Opioid epidemic in the USA. Lessons learned…

David Sidebotham

Auckland City Hospital, New Zealand

Case and Deacon

On 8th December 2015 a remarkable paper was published in the *Proceedings of the National Academy of Sciences*.[1] The authors were Anne Case and Angus Deacon, a husband and wife team from the Woodrow Wilson School of Public and International Affairs, Princeton University. Anne Case is a Professor of Economics and Public Affairs and Sir Angus Deacon is the Dwight D. Eisenhower Professor of International Affairs and Professor of Economics. He is also the winner of the 2015 Nobel Prize in Economics. Their paper, entitled, "Rising Morbidity and Mortality in Midlife Among White, Non-Hispanic Americans in the 21st Century", identified an increasing death rate amongst white Americans – particularly whites with limited education in their middle years –a trend beginning in the late 1990s and continuing to the present day. Over the same time period, death rates for Hispanics and blacks in the United States (US) continued to decrease, as did death rates for adults in other first world countries. Case and Deaton identified three causes of the increase: chronic liver disease, suicide, and, most importantly, poisonings. While such a trend in a first world country during peacetime is not unprecedented – it happened in Germany following the Second World War and in Russia after the fall of the Soviet Union – it is, nevertheless, highly unusual. The authors commented that, while the causes are incompletely understood, there was a strong link to the increased availability of opioid prescriptions during the same time period.

Case and Deacon's paper received considerable attention in the media. "The Dying of the Whites" (Ross Douthat, *New York Times*, November 7, 2015), "Middle-Aged White Americans are Dying of Despair" (Olga Khazan, *The Atlantic*, November 4, 2015), and "Why Are So Many Middle-Aged White Americans Dying?" (Olga Khazan, *The Atlantic* January 29, 2016) are three examples, but there are 100s of such essays to be found online.

Just how bad is it?

Over the last two years, in both the medical literature and the media, the excess mortality amongst poorly educated whites, first identified by Case and Deacon, has been increasingly linked to opioid overdose. One of the most compelling articles addressing rising mortality from drug overdose is from Josh Katz. In an article "Just How Bad is the Drug Overdose Epidemic?", published in the *New York Times* in April of this year, Katz quotes figures from the National Center for Health Statistics, Centers for Disease Control and Prevention.[2] Katz identifies 52,404 deaths from drug overdoses in 2015, up from 8413 in 1990, a 500% increase. The figure of 52,404 compares to 37,757 deaths from car accidents, 35,763 from guns, and 6,465 from HIV/AIDS in the same year. Given that approximately 60% of gun deaths are from suicide, in 2015 deaths from drug overdoses exceeded that of gun homicide and car accidents combined, and the rate of increase in overdose deaths is similar to the death rate increase during the worst period of the HIV/AIDS epidemic in the late 1990s. Drug overdose is now the leading cause of death in people under 50 in the US. In short, the current drug epidemic is the worst in US history.

Unlike other recent drug crises, such as crack cocaine in the 1980s and methamphetamine in the early 2000s, this epidemic involves opioids, most commonly taken in the form of prescription drugs – oxycodone (OxyContin, Percocet) and hydrocodone (Vicodin) – or as heroin. More recently, illegally imported fentanyl and other synthetic opioids have become more common.
The epidemic has a very uneven geographic distribution.[2,3] The worst affected regions are the rural, socially disadvantaged, parts of Appalachia (West Virginia, Kentucky, Pennsylvania, and southern Ohio)

and New England (New Hampshire, Massachusetts, and Maine). In the worst affected state, West Virginia, the death rate during 2014-2015 was approximately 40 per 100,000 people.[3] During the same time period, the death rate in Nebraska, the 25th worse state, was approximately 7.5 per 100,000 people. Within West Virginia itself the death rate during 2014-2015 varied from county to country, from less than 10/100,000 to more than 130/100,000 deaths per persons, being concentrated in poorer, more rural communities. Again, the concentration in rural communities is in contradistinction to urban-based drug problems of the past: The New York heroin scene of the 1960s and 1970s and the crack cocaine epidemic of the 1980s, which occurred predominantly in poor parts of large urban centres, such as Chicago and Detroit.

Porter and Jick

In 1980, a one paragraph letter appeared in the *New England Journal of Medicine* under innocent-sounding title, "Addiction Rare in Patients Treated with Narcotics".[4] In it, Jane Porter and Hershel Jick, from the Boston Collaborative Drug Surveillance Program, briefly outlined how they encountered only four documented cases of addiction (only one of which was "severe") amongst 40,000 hospitalised patients, of whom 12,000 received at least one opioid prescription. The authors didn't describe any post-hospital follow-up (there wasn't any) and did not describe their methodology. However, the figure – less than 4 in 12,000 patients – transmogrified into a widely quoted figure of "less than 1% risk of addiction".

Six years later Russell Portenoy and Kathleen Foley, writing in the journal *Pain*, described treating 38 patients with opioid analgesics for chronic, non-malignant pain,[5] a practice that had hitherto been rare. These two papers were picked up by the media. Ronald Melzack, writing in *Scientific American* in 1990 under the title, "The Tragedy of Needless Pain",[6] wrote, "Contrary to popular belief, morphine taken solely to control pain is not addictive. Yet patients worldwide continue to be undertreated and to suffer unnecessary agony". Sam Allis, writing in *Time* magazine in 2001 in an article entitled "Less Pain, More Gain" described Porter and Jick's one paragraph letter as a "landmark study" and claimed it demonstrated that, "The exaggerated fear that patients would become addicted to opiates was basically unwarranted".[7] Russell Portenoy, being interviewed in the *New York Times* in 1993 claimed, "There is a growing literature showing these drugs (opioids) can be used for a long time with few side-effects and that addiction and abuse are not a problem".

And so, from these humble beginnings, and in the absence of any meaningful evidence of safety, opioid prescribing for chronic non-malignant pain commenced in earnest. Prescriptions for opioid analgesics increased three-fold between 1999 and 2010, a 10-year period (data from the US Annual review of Health). During the same time period, deaths from opioid overdoses increased four-fold and admissions for opioid treatment increased three-fold.

As befitting a bona-fide treatment, in 2009 clinical guidelines for the use of chronic opioid therapy for chronic non-cancer pain were published.[8] While taking a relatively favourable position to the use of opioids for chronic, non-cancer pain, the guidelines have very little to say on the risks associated with such therapy. They do state, however, that, "Estimates of aberrant drug-related behaviours, drug abuse, or misuse in patients range from 0% to 50%" (!). In the disclosures, 11 of the 20 authors report receiving industry-sponsored research funding and 12/20 list having received industry honoraria, including the now famous, Russell Portenoy.

In fact, chronic pain *is* a serious unmet need in the US. In a 2010 survey of 90,000 patients, one in five respondents – equating to 39 million US citizens – described having persistent pain, defined as pain on most days for longer than three months.[9] Unfortunately, it is increasingly apparent that using opioids to treat chronic non-cancer pain is harmful, over and above the risk of overdose. In a recent article in *JAMA* patients treated with long-acting opioids for chronic, non-cancer pain had an increased mortality

compared to propensity matched controls, including for non-overdose deaths (Hazard ratio 1.72, 95% confidence interval 1.24-2.39).[10]
By 2011, in the thick of the prescription opioid crisis, Russell Portenoy had had a change of heart. In an interview released by Physicians for Responsible Opioid Prescribing he had this to say: "None of the papers presented any real evidence, and yet what I was trying to do was create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids…because the primary goal was to destigmatise we often left the evidence behind".

Purdue Pharma: an American success story

Purdue Pharma is a privately owned pharmaceutical company founded in 1952 and based in Stamford Connecticut. Purdue began life innocuously enough producing laxatives, earwax remover, and antiseptics. However, in 1991 Purdue began focussing on pain management, in particular oral formulations of opioid analgesics. It has on its books MS Contin (morphine), Dilaudid (hydromorphone), Butrans (buprenorphine), and – the 900-lb gorilla of them all – OxyContin (sustained release oxycodone). Concurrent with the shift to 'pain management' Purdue's fortunes have blossomed. By 2015 *Forbes* magazine estimated Purdue was worth USD $35 billion. Growth has come almost exclusively from sales of opioid analgesics, most importantly OxyContin. The company is privately owned by the Sackler family. Again in 2015, *Forbes* 'conservatively' estimated their wealth at USD $14 billion, money made almost exclusively from Purdue and its sale of OxyContin.

OxyContin was approved by the FDA in 1996 and marketed as a safe alternative to other opioids for patients with moderate and severe pain. The long-acting formulation was touted as avoiding the intense high sought by addicts and it was claimed to be 'nearly addiction proof'. In its first year of release, US sales of OxyContin generated USD 44 million, a figure that had increased to a whopping USD 1.5 billion/year by 2002.[11,12] These figures represent only US sales; the drug is sold in more than 35 countries world-wide.

Unfortunately, OxyContin is not as safe as initially advertised. It turns out that crushing the tablets released up to 70% of the free oxycodone, information that had long been known from Purdue's in-house testing. Given the high tablet strength (up to 160 mg) the drug became a ready source of strong opioid for snorting or injecting. Recreational use, addiction, overdose, and death became widespread.

The methods by which Purdue went about marketing OxyContin have been well documented, both in in the medical literature[13] and the mainstream media.[14] In an article from *American Journal of Public Health*, entitled, "The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy", Art Van Zee lays bare the techniques used by Purdue. First and foremost, OxyContin was promoted for non-cancer pain. While the number of patients with cancer pain is relatively static, as noted above, 39 million Americans suffer persistent pain. Second, Purdue targeted primary-care physicians. Previously, long-term opioid prescribing was the domain of palliative care physicians and oncologists. However, by 2002 half of all opioid prescriptions were by written by primary care physicians, many of whom had little training in the safe prescribing of opioids. To achieve these goals, Purdue funded all-expenses paid 'pain management' conferences to resorts in California, Arizona, and Florida. More than 5,000 doctors, nurses and pharmacists attended these meetings, where they were 'trained' in pain management by Purdue's bureau of experts. Marketing giveaways included soft toys, fishing hats, multi-tools, and, curiously, a compact disc of swing music ("Get in to the Swing of it with OxyContin"). Between 1996-2002 the OxyContin sales force doubled and sales representatives were paid bonuses averaging USD $70,000/year. Some received bonuses as high as high as USD $250,000/year. Patients were given free OxyContin 'starter packs' of between one week and one month's supply. In total, 36,000 starter packs were distributed. Throughout it all, Purdue systematically downplayed the risk of addiction, frequently citing the inherent safety of the slow release formulation and the "less than 1% risk of addiction" misquote from Porter and Jick. As Mike Mariani wrote in *The New York Times*, "It

was the most aggressive marketing campaign ever by a pharmaceutical company for a narcotic painkiller".[14]

However, by the early 2000s concerns were increasing about problems of addiction, overdose, and death related to prescription opioids, and with OxyContin in particular. In 2003 Purdue Pharma was the subject of a Congressional investigation by the US General Accounting Office.[11,12] Its report found Purdue had pursued an aggressive marketing campaign promoting the drug to treat a range of conditions to physicians who may not have been adequately trained in pain management. Purdue was cited for false and misleading advertising, particularly relating to minimising the abuse potential and risk of overdose associated with OxyContin. In 2007, this led to a federal law suit, in which Purdue entered into a plea agreement, admitting charges that it misled doctors and patients about the addictive properties of OxyContin and misbranded the product as "abuse resistant." Purdue was fined USD $634 million, and various executives including Michael Friedman (president) and Paul Goldenheim (medical director) were subject to multi-million dollar personal settlements. The figure of USD $634 million, while substantial, pales when compared to the more than USD $10 billion Purdue made from OxyContin during its first six years of sales and the estimated USD $72.5 billion annual cost to health insurers of the opioid epidemic. Subsequently, tight restrictions have been placed on opioid prescribing in the US and there have been numerous high-profile convictions of doctors found guilty of reckless prescribing. Sentences have involved lengthy prison time. OxyContin itself has now been re-formulated by Purdue to reduce the release of free drug when crushed. Ironically, this has allowed Purdue prolonged patent protection for OxyContin. Despite a lull during the years 2004-2006, sales of OxyContin subsequently increased and have remained above USD $2 billion annually. To date, OxyContin have generated in excess of USD $25 billion for Purdue.

The ascendancy of heroin and fentanyl

Since 2011 deaths from prescription opioids has decreased slightly. However, overall deaths from drug overdose have continue to increase, largely on the back of a dramatic increase in deaths related to heroin and fentanyl. A key reason for this change has been the fall in price and increased availability of heroin and fentanyl. In inflation-adjusted dollars, the price of heroin fell from USD $3,260/gram in 1981 to USD $465/gram in 2012 (data from US Offices of National Drug Control Policy).

One contributor to the falling price of heroin is a softening of the approach to cannabis by US lawmakers. Unlike most of the world, which sources its heroin from Afghanistan, only 4% of US heroin comes from Central Asia. Most of the US heroin comes across its southern border, either directly from Mexico or indirectly from Columbia. In particular, there has been a dramatic rise in the cultivation of opium poppies in the Sierra Madro region of Mexico. Increased legal production of cannabis in the US has dramatically reduced the profitability of Mexican-grown cannabis, causing farmers and cartels in the hill country of Sinola state (of the Sinola cartel and El Chappo fame) to shift to heroin production.

In drug addicted America, cheap heroin has filled the gap left by the reduced availability of prescription opioids. Today in the US, it is easier and cheaper to purchase an equivalent dose of heroin than 'oxy'.

And not just heroin. Fentanyl and other synthetic opioids, such as U-47700 ('Pink'), furanyl fentanyl, and carfentanil, have begun appearing in the US. These drugs are virtually all purchased online (via the so-called 'dark web' or TOR (the onion router) network), largely from China, and brought into the US by the postal service. The move from prescription drugs to heroin and fentanyl has come at significant cost in terms of inadvertent drug overdose and death. While not ideal, at least when crushing OxyContin, addicts are using a product that has been prepared to an industry standard by professionals with a reasonable training in pharmacology and weights and measures. No such guarantee is available when dealers cut 'oxy' and heroin with fentanyl and carfentanil.

With a potency of 10,000 times that of morphine, carfentanil, is a particularly dangerous drug. Carfentanil is available commercially for use by vets for anaesthetising large animals, such as elephants. The human LD 50 of carfentanil is as little as the equivalent of one grain of salt. Carfentanil is easily absorbed through the skin, and there have been several deaths of law enforcement officers (and vets) following inadvertent skin exposure. Even the clandestine labs in China who manufacture the drug state on their websites that carfentanil should only to be taken by 'experienced fentanyl users'.

Social decay, unemployment, and Trumpland

The communities that have been worst affect by the opioid epidemic are some of the poorest in the country. Blue collar counties that have suffered greatly from the decline of industry in the US over the last three decades. Communities affected by factory closures, shuttered-up businesses, and social decay. Unemployment is high, rates of health insurance are low, and alcoholism, suicide, and drug addiction are rife. These are the same communities that overwhelmingly voted for Donald Trump in the 2015 presidential election.

A multi-faceted approach is required to solve the current crisis, including good jobs, decent wages, increased educational achievement, and a much greater availability and funding of drug rehabilitation programmes. Whether or not building a wall along its southern border, trade tariffs aimed at bringing back American jobs, and repeal of the Affordable Care Act will achieve these ends is a matter of debate. To this observer, at least, such an outcome seems unlikely.

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