

**REVIEW ARTICLE**

**The current opioid epidemic – a re-examination of all of its causes**

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**Abstract**

Currently, we are experiencing an opioid prescription drug epidemic and the deadly and addicting drugs, overprescribing physicians, deceiving pharmaceutical companies and the government are blamed for this tragedy. However, while all of these have contributed albeit in a minor way to the epidemic, the real cause is never mentioned – namely the drug abuser per se. It has to be realized that certain individuals who are genetically programmed and environmentally influenced will abuse drugs – as they have done so in the past, doing it now and will be doing so in the future. This paper examines in some detail all of these five factors with recommendations to perhaps minimize this and future epidemics.

**Keywords**

Opioids – opioid drugs – physician – pharmaceutical companies – government – drug abuser

## **Introduction**

At present – as told by the lay but also the professional press – we are experiencing a narcotic prescription epidemic causing a large number of unwanted deaths. Also, we are quickly told that the epidemic is caused by addictive and deadly narcotic drugs, by deceiving and unethical advertisements of certain pharmaceutical companies, by unprofessional and uneducated pain killer prescribing by physicians and the usual lack of interventions by our government. However, some of these assumptions and accusations are in need of some corrections and clarifications to obtain a better and more accurate picture of the current drug situation and perhaps of drug abuse per se. Thus, here are some of the particulars to be considered.

## **The current epidemic**

One of the first questions to be asked is: do we really have a prescription drug epidemic involving drugs like morphine, oxycodone and hydrocodone and others? While prescription drugs are indeed abused by a large number of individuals, their abuse and related deaths are smaller as compared to those of other substances and drugs. The substances abused by more individuals are alcohol, cocaine and methamphetamine and they are 2-4 times more involved in substance related deaths than, for instance, oxycodone and hydrocodone (1-4). As

an example, the Florida medical examiners reported for 2016 the following sequence of drugs involved in drug overdose deaths as ethanol, fentanyl and its analogs, cocaine, benzodiazepines, heroin followed by oxycodone and hydrocodone. Focusing on prescription drug abuse instead is most likely due to the fact that such an abuse is relatively new and provides us easily with someone to blame (and to sue and indeed the first law suits have already been filed) like physicians, the pharmaceutical industry and the government while ethanol abuse problems are more forgiving since most of us are social drinkers and we have gotten used over the decades to cocaine and methamphetamine abuse and its heavy toll on human lives. Nevertheless, accepting the current opioid prescription drug epidemic, history has taught us that such epidemics have occurred also in the past but also did subside like the epidemics of opium abuse in China, the post civil war morphine addiction, laudanum use during the Victorian age and heroin abuse crisis in the 70/80s. Fortunately, today's epidemic of prescription drug abuse will like all epidemics also eventually reside (and most likely reoccur or be replaced by another drug epidemic in the future).

## **What is addiction?**

The word addiction is too often used and many times with a wrong meaning. Addiction has many definitions with the most medically relevant being outlined in the DSM-5 (which unfortunately calls it dependence which can easily lead to confusion as can be seen later). Basically, addiction is characterized by an uncontrollable craving for a drug or substance (in this case an opioid), to be used continuously to obtain pleasure (“rush” or “high”) or to avoid displeasure (withdrawal discomfort) which eventually leads to harmful and destructive personal, professional and social consequences. In the case of opioids, the occasional, controlled use of an opioid is not considered addiction and even more frequent uses while an individual is still functioning well socially and professionally should not be considered addiction but a poorly controlled abusive behavior. Furthermore, addiction should not be confused with physical dependence or tolerance. Opioids and other illegal or legal drugs all can cause the same pharmacological effects. Fortunately, physical dependence to opioids usually carries no significant health consequences while the withdrawal syndrome can be quite discomforting (but is still considerably milder than that which is experienced with alcohol withdrawal which can be fatal). Similarly, tolerance often cited as a danger of opioid use is not unique to these drugs and can be

observed with other drugs as well. Thus, addiction has a very special meaning and can occur, of course, with many substances or drugs. The cause of drug or substance addiction in general can be viewed in 2 ways in that 1) drug use leads secondarily to addictive behaviors or 2) addictive personalities do secondarily abuse drugs. The first is often believed by lay people while medical and scientific people accept the second (5).

### **What are addictive drugs?**

The use of “addictive drugs or in this case “addictive opioids” is often used but is misleading and should not be used at all. It implies wrongly that the main effect of the drug is to cause addiction like a general anesthetic causes anesthesia, an anti-allergic drug suppresses an allergic reaction or a pain killer will reduce or eliminate pain in all of its users. This, of course, is not the case with opioids who when used properly will not lead to addictive consequences in the vast majority of patients and users. It is a small minority which do use, misuse or abuse them improperly and eventually become addicted (6-8). This is like the allergic reaction of a person to peanuts. We would not call peanuts “allergy provoking nuts”. Peanuts do not cause allergies in most individuals unless they are ingested by an individual with a particular idiosyncrasy of his/her immune system. Here, it is this

biochemical peculiarity which causes the allergic reaction when exposed to peanuts. Thus, an opioid is just an opioid which should be named an analgesic opioid or narcotic analgesic with the warning that it can be abused by a small number of individuals who possess certain addictive personality vulnerabilities.

### **Safety of opioid or narcotic prescription drugs**

Opioids or narcotic analgesics are often labeled as being extremely toxic and deadly due to the large number of overdose deaths which occur with their use. Again, opioids like morphine, oxycodone, hydrocodone and heroin are actually relative safe drugs. Their major problems when used properly are nausea, vomiting, constipation, some cognitive effects plus some other relative minor problems. If used properly, even long term physical and mental effects seem to be moderate as evidenced by case reports involving health professionals who had access to the pure substance or drug and showed little health effects even after long term use. For instance, a physician who had abused morphine for 62 years was found to be in good physical and mental health at the age of 84; a physician who confesses that he injects morphine daily before seeing patients is productive and in good health; and the “father of scientific surgery”, Dr. William Halstedt, who used both morphine and cocaine for his entire professional career

without any obvious mental or physical problems (9-12). The latter also demonstrates that the misuse of an opioid is not necessarily incompatible with any constructive professional activity by knowledgeable individuals. While scientific studies using brain imaging do find certain abnormalities, they, however, do not seem to be of major clinical importance and it is often difficult to discern if they were caused by the drug or if they already had existed before a drug was used (13-15). If these drugs including heroin are relatively safe, why do people die of these drugs? The reason is quite simple – individuals who experience major health problems or even die do either not use them as directed or obtain them from illegal sources. The latter is often a major factor since such illegal preparations are of uncertain origin, quality and dose and are often mixed with other substances which again are of uncertain quality and dose. Toxicological reports from individuals who have died of overdoses generally show that they had ingested a number of different drugs and substance including various opioids, benzodiazepines, cocaine, methamphetamine, fentanyl and its analogues and/or alcohol. A survey of, for instance, toxicological screens of drug deaths in Florida as well as a detailed analysis of such deaths in one of its counties over the last 10 years reveals that there was no definitive evidence that an individual had died of a regular dose of a single

prescription opioid but the vast majority died because in addition of a prescription drug they had other drugs in their bodies in some cases up to 12 other drugs (17-20). In particular, the more recent adulteration of illegal opioids with fentanyl, carfentanyl and related analogues which are exceedingly potent with an extremely narrow margin of safety plays a major role in causing such recent deaths (3, 21-23). Thus, opioid drugs are relatively safe if used properly and even used long term albeit any drug taken for long periods of time and at high doses will cause some unwanted often serious effects in some of its users. However, opioids used improperly, in combination with other drugs or substances or obtained illegally can and are extremely dangerous and do account at present for almost all of the reported deaths.

### **Physicians**

Physicians are also accused and blamed to be responsible for the opioid epidemic by overprescribing these opioid drugs. This is mostly based on the correlation between the number of opioid prescriptions written and the number of opioid users and deaths. However, correlations are no cause and effect and a survey of these reports is not so clear-cut. For instance, one survey places Alabama as one of the states with lower prescription numbers while another report places this state on the top. Similarly, the District of Columbia has only a relatively moderate drug prescription rate but is placed

highest on opioid abuse problems and deaths (24-28). Another caveat is that the number of opioid prescriptions has declined in recent years, after federal regulators placed new limits on prescribing these drugs. In 2010 prescription writing peaked and declined slowly thereafter while the opioid epidemic was only moderate at this time and increased thereafter (29). Many individuals fill drug prescriptions but never use them. A personal brief survey of the author of 95 retired individuals who had been prescribed a narcotic after an operation found that all had bought the drugs but two thirds never used them and none was found to have a drug problem. Nevertheless, there is a correlation pointing to overprescribing but it is indirect and weak to moderate at best. However, there are some reports which more directly point to the fact that some physicians might have indeed overprescribed (30,31). The extent of this is uncertain and it usually involves a prescription for 30 days were in many instances 10 days would have sufficed. It also has to be considered that there are about 25 million adult Americans who experience daily pain with the associated suffering, disabilities, loss of work productivity, loss of quality of life, and reduced overall health status (32) and physicians have a fundamental duty to relieve pain which most physicians follow (33,34). Furthermore, it is well known that pain cannot be measured and truly assessed except as obtained from the

words and behavior of the patient. In addition, many patients during their visits demand drugs from their physicians who then might yield to this pressure (35) Thus, physicians in order not to deprive a patient of necessary pain relief, might have erred in favor of believing and trusting the patient. This might have been aided by the fact that physicians in the past had been told that they had under prescribed pain medication and now felt that they had to correct this problem by being somewhat more broadminded. All of this, of course, now opened the door for the abuser who often fools the physician with faked pain (36). However, being too careful could lead to depriving the patient who do not abuse but need these medications for their pain relief (37). Furthermore, the vast majority of patients uses these drugs properly and is aware of the slight possibility of becoming addicted (39-40). Nevertheless, physicians must still be better informed, for instance, in being aware that opioids are often a poor choice for most chronic pains and physicians should look for available alternatives or to prescribe 10 pills instead of 30 (41). The next question is how many of their patients have become abusers and addicted by being prescribed an opioid drug? One of the earlier papers from 1980 states that a survey of 11 882 patients found that only 4 people developed an associated abuse problem (42). More recent reports show that the risk of

patients developing an opioid problem with a history of prior substance abuse is about 5-10% while the risk of individuals without prior substance abuse is about 1 % (43). And even if the physician would not have prescribed an opioid drug to an abuser, that individual would have obtained heroin on the street which could have been even more harmful or even deadly (44, 45). Similarly, the suggestion that the prescription of an opioid drug by a physician without prior abuse problems would lead to the initiation of opioid abuse is very weak since many studies find that first time users obtained these drugs from friends or family (46-49). In conclusion, overprescribing by ethical physicians does not seem to have been a large factor in initiating or maintaining the current opioid crisis.

### **The pharmaceutical companies**

The pharmaceutical industry is mostly blamed for the opioid epidemic by marketing such opioid drugs. First of all, these drugs are exceedingly beneficial in treating many non-cancer and cancer related pains and help many individuals to resume almost normal activities or die relatively pain free and without major discomfort. However, they are blamed for marketing these drugs with false advertisements to physicians in that these drugs were claimed to be long acting and not or only mildly addicting. In the beginning of introducing these

drugs, there was indeed some basis for this claim. At this time it was generally assumed that the abuse liability was lower in long- than in short-acting opioids because long-acting drugs cause lower serum drug levels which are less likely to induce pleasurable psychoactive effects. Furthermore, the FDA had approved these drugs. However, it was soon determined that even long acting preparation carried a risk of being abused (50, 51). However, as such evidence emerged companies suppressed these detrimental findings and for this, one company and three of its executives later pleaded guilty and were fined and paid about 634 million dollars (52). However, the evidence of these drugs to initiating and maintaining addiction is relative small as seen above. Only a very small number of prescription drug users will progress to abusers and many of them already had a history of substance and drug abuse. But these companies cannot be held responsible for the deaths due to the use of their drugs. If an individual would have used them as recommended, this individual might have experienced some adverse reactions but would not have died. However, if the user did not follow the instructions and ingested higher doses of a drug as recommended, altered an oral preparation into an injectable one, used it with other drugs or bought them illegally from unknown sources, then these drugs could indeed be fatal. However, for this, companies

cannot be held responsible. This is similar to the practice of many companies which make the statement if their products are not used according to instructions or have been altered by non-authorized people than the company will not be responsible for any detrimental consequences of their products. Even the claim that they should have made fool proof drug preparations which could not be abused – which companies tried to do – would not have succeeded because abusers will always find a way around it like the hacker who eventually will break into the most secure computer system. Thus, the pharmaceutical industry might have contributed in a minor way to the epidemic but certainly not to the staggering number of deaths caused by their drugs.

### **The government**

The last to blame is the government which should have intervened and prevented or minimize the opioid problem. Unfortunately, governments with best intentions have historically been shown to be of little help and in some cases to do even more harm than good. In the past, governments always tried to intervene by introducing new and tougher laws, increasing the narcotic divisions of the police force, incarcerating more individuals and forever longer times, declaring a “War on Drugs” and spending millions of dollars on advertising about the danger of abusing drugs.

But all these efforts have failed and drug abuse has and is still flourishing. More recently, 11 times more people were jailed for drug offenses in 2015 than in 1980 and the current opioid epidemic still occurred (53). Thus, preventing or reducing drug abuse by laws does not seem to work. The government has to realize that addiction is a disease and a medical problem which has to be dealt with and helped by the medical profession and not the government albeit the latter can help financially. What is unacceptable is that as the Wall Street Journal reported on January 5, 2018, that a high official of the justice department voiced an opinion about a drug because “he felt” that it is highly addictive. The government cannot prevent or cure a flu epidemic but it can force people to get flu shots. Thus, the government can do certain actions which might be helpful to reduce drug abuse. First, improving the economic conditions of the less privileged population might help since drug abuse has been shown to be more prevalent among the unemployed and underprivileged (54, 55) Second, funding for rehabilitation of addicted individuals can be increased which is still inadequate with perhaps only about 10% of addicted individuals receiving needed medical or psychological help (56). Third, increasing the availability of naloxone and make its use more open to counteract an impending overdose (57). Fourth, it might be wise to look

at other countries how these governments deal with their drug abuse problems. A case in point is Switzerland. Here, heroin addicts are first treated with methadone and if this therapy does not work, a heroin user can obtain heroin legally. This approach has reduced crime rates, has caused fewer health problems including overdose deaths due to illegal heroin and has led to a productive professional life for many of these individuals since its inception (58, 59). Thus, governments can actually do very little to prevent or control drug abuse but still could minimize its extent and prevent unwanted deaths by better laws.

### **The opioid drug abuser or addict**

The question now arises if all of the above did not contribute in a major way to the epidemic, why do we have drug abuse problems and drug deaths? The answer is: the individual who abuses drugs is the main cause. And indeed most evidence points to him or her. It appears that one component of the human personality is the desire to use substances to experience pleasure and/or to avoid pain and discomfort (60). History tells us that the use and abuse of certain substances is age old and covers most geographical areas of this globe with alcohol already being mentioned about 7000 years and opium about 3000 yrs ago. For instance, the old Sumerians already used the poppy plant for various reasons and called it “plant of joy”

indicating that they were aware of its pleasing psychoactive effects (61). This desire to use and to finally abuse substances and drugs, however, is now believed by most neuroscientists to depend on the balance between the desire for pleasure or the relief of discomfort and the will power of an individual. Neuroscience places the pleasure and discomfort avoidance drives mostly in the reward center like the nucleus accumbens and the will power or control mostly in the prefrontal cortex (60, 62, 63). Thus, there will always be some individuals which have a high desire for quick reward coupled with weak will power which places them at risk to become addicted. These neuronal centers are genetically determined but can be influenced by

environmental factors albeit not overruled (64). Since we cannot change an addictive prone genome of a future drug abuser and since environmental conditions will fluctuate from favorable to unfavorable, it can be assumed that there will always be some individuals who will abuse drugs or substances. Thus, addiction problems have been with us in the past and will be with us in the future and the best we can hope for is to minimize this problem.

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## References

1. [https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates,](https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)
2. [https://www.ncbi.nlm.nih.gov/pubmed/28177817;](https://www.ncbi.nlm.nih.gov/pubmed/28177817)
3. <http://www.fdle.state.fl.us/MEC/Publications-and-Forms/Documents/Drugs-in-Deceased-Persons/2015-Annual-Drug-Report.aspx;>
4. [https://www.ncbi.nlm.nih.gov/pubmed/21708436\).](https://www.ncbi.nlm.nih.gov/pubmed/21708436)
5. L Squire, D. Berg, F.E. Bloom, S. du Lac, A. Ghosh, N. C. Spitzer, L. R. Squire, *Fundamentals of Neuroscience*, 3rd edition, Elsevier Publisher (2012) – Addiction, pp.999 -1031, 2012
6. <https://www.ncbi.nlm.nih.gov/pubmed/29049118>
7. [https://www.google.com/search?q=addiction+risk+drugs&oq=addiction+risk+drugs&aqs=chrome.69i57j0.7140j0j7&sourceid=chrome&ie=UTF-8;](https://www.google.com/search?q=addiction+risk+drugs&oq=addiction+risk+drugs&aqs=chrome.69i57j0.7140j0j7&sourceid=chrome&ie=UTF-8)
8. [https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-abuse-addiction\)](https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-abuse-addiction)
9. [http://www.nytimes.com/2010/04/27/health/27zuger.html;](http://www.nytimes.com/2010/04/27/health/27zuger.html)
10. [https://www.ncbi.nlm.nih.gov/pubmed/12855350,](https://www.ncbi.nlm.nih.gov/pubmed/12855350)
11. [https://www.express.co.uk/expressyourself/193268/A-drug-addict-doctor-speaks-out;](https://www.express.co.uk/expressyourself/193268/A-drug-addict-doctor-speaks-out)
12. [http://www.druglibrary.org/schaffer/library/studies/cu/cu5.html\).](http://www.druglibrary.org/schaffer/library/studies/cu/cu5.html)
13. <https://www.ncbi.nlm.nih.gov/pubmed/15610908>
14. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912691/>
15. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036624/>
16. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3454351/;](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3454351/)
17. [https://www.theguardian.com/us-news/commentisfree/2016/jun/08/opioid-epidemic-drug-mix-overdose-death;](https://www.theguardian.com/us-news/commentisfree/2016/jun/08/opioid-epidemic-drug-mix-overdose-death)
18. [https://www.dea.gov/docs/DEA-PHL-DIR-03417%20Analysis%20of%20Overdose%20Deaths%20in%20Pennsylvania%202016.pdf;](https://www.dea.gov/docs/DEA-PHL-DIR-03417%20Analysis%20of%20Overdose%20Deaths%20in%20Pennsylvania%202016.pdf)
19. <https://www.nytimes.com/interactive/2017/09/02/upshot/fentanyl-drug-overdose-deaths.html>
20. [https://www.theatlantic.com/business/archive/2017/06/lawsuit-pharmaceutical-companies-opioids/529020/\).](https://www.theatlantic.com/business/archive/2017/06/lawsuit-pharmaceutical-companies-opioids/529020/)
21. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3454351/;](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3454351/)
22. [https://www.theguardian.com/us-news/commentisfree/2016/jun/08/opioid-epidemic-drug-mix-overdose-death;](https://www.theguardian.com/us-news/commentisfree/2016/jun/08/opioid-epidemic-drug-mix-overdose-death)<https://www.dea.gov/docs/DEA-PHL-DIR034>

23. [17% Analysis of Overdose Deaths in Pennsylvania 2016.pdf](#)
24. <http://247wallst.com/special-report/2016/06/24/10-states-with-the-most-drug-overdoses/>,
25. <https://www.cdc.gov/vitalsigns/opioid-prescribing/>;
26. <http://www.moveforwardpt.com/Resources/Detail/opioid-abuse-statistics-of-50-states>
27. <https://www.statista.com/statistics/686415/top-ten-leading-states-concerning-death-rate-of-drug-overdose-in-the-us/>
28. <https://ranchatdovetree.com/blog/highest-abuse-prescription-drugs/>.
29. <https://www.npr.org/sections/thetwo-way/2017/09/19/552135830/41-states-to-investigate-pharmaceutical-companies-over-opioids>
30. <https://www.webmd.com/pain-management/news/20170731/doctors-still-overprescribing-opioids-in-us#1>
31. <https://www.cdc.gov/drugoverdose/data/prescribing.htm>
32. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509148/>
33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325448/>;
34. <https://www.fiercehealthcare.com/healthcare/er-physicians-don-t-overprescribe-opioids-study-finds>).
35. <https://psmag.com/news/experts-are-only-cautiously-optimistic>).
36. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3073133>
37. <https://www.vox.com/science-and-health/2017/4/7/14738292/crackdown-opioid-prescriptions-chronic-pain>
38. <https://www.webmd.com/pain-management/features/pain-medication-addiction#1>;
39. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494184>
40. E.Metcalf. Pain Medication: Are You Addicted? WebMD June 19,2012 <http://www.webmd.com/painmanagement/features/pain-medicationaddiction#1>
41. [https://www.medscape.com/viewarticle/861351\\_2](https://www.medscape.com/viewarticle/861351_2)
42. <http://www.businessinsider.com/porter-and-jick-letter-launched-the-opioid-epidemic-2016-5>).
43. pubmedpub
44. <https://www.drugabuse.gov/publications/research-reports/relationship-between-prescription-drug-heroin-abuse/heroin-use-rare-in-prescription-drug-users>;
45. <https://www.drugabuse.gov/publications/research-reports/relationship-between-prescription-drug-abuse-heroin-use/heroin-use-driven-by-its-low-cost-high-availability>

46. <https://obamawhitehouse.archives.gov/blog/2012/04/25/friends-and-family-are-primary-sources-abused-prescription-drugs>
47. <https://www.cdc.gov/media/releases/2014/p0303-prescription-opioids.html>;
48. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1706073/#!po=56.6667>;
49. <http://painandpsa.org/the-opioid-epidemic-a-brief-history/>.
50. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757543/>
51. <https://www.orlandorecovery.com/long-term-addiction-treatment-maintenance/correlation-drug-half-life-medicines/#gref>
52. <http://www.nytimes.com/2007/05/10/business/11drug-web.html>
53. <https://www.popsoci.com/science/article/2013-04/which-drugs-actually-kill-americans>
54. <https://www.popsoci.com/science/article/2013-04/which-drugs-actually-kill-americans>
55. <https://www.sciencedirect.com/science/article/pii/S0955395917300877>
56. <https://www.drugabuse.gov/publications/drug-facts/treatment-approaches-drug-addiction>
57. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm>.
58. <http://www.citizensopposingprohibition.org/resources/swiss-heroin-assisted-treatment-1994-2009-summary/>
59. <http://druglawreform.info/en/issues/harm-reduction/item/1272-the-impact-of-heroin-prescription-on-heroin-markets-in-switzerland>
60. Vogel, W H : A qualitative and semi-quantitative combined theory of addiction. *Medical Research Archives*. Volume 5, issue 9. September 2017.
61. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202501/>.
62. <http://www.dana.org/Publications/ReportDetails.aspx?id=44208>;
63. <https://www.ncbi.nlm.nih.gov/pubmed/27363441>
64. <https://www.ncbi.nlm.nih.gov/pubmed/16173210>.