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SPECIAL ARTICLE

Historical analysis of opioids epidemic in United States of America (Part II)

Análisis histórico de la epidemia de opioides en Estados Unidos (Parte II)

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ABSTRACT:

The work conducts a review of the most relevant historical facts that have occurred in the United States regarding the use of opioids in the treatment of pain. This analysis is relevant to identifying what events may have caused or contributed to the onset and development of the current opioid epidemic in the United States. We also conduct an analysis and discussion of the measures that have been taken in the United States in relation to this epidemic. In this second part, we analyzed the developments and measures implemented in the United States between 2010 and 2018.

RESUMEN:

En este trabajo se realiza una revisión de los hechos históricos más relevantes ocurridos en Estados Unidos en relación con el uso de los opioides en el tratamiento del dolor. Este análisis es relevante para identificar cuáles han podido ser los eventos que hayan causado o contribuido al inicio y desarrollo de la actual "epidemia" de consumo de opioides en Estados Unidos. Asimismo, realizamos un análisis y discusión de las medidas que se han tomado en Estados Unidos con relación a esta epidemia. En esta segunda parte, analizamos los acontecimientos y medidas implementadas en Estados Unidos entre los años 2010 y 2018.

Introduction

Historical analysis of pain management and prescription opioid use is relevant to understanding what events and causes have been likely to contribute to the onset and development of the current epidemic in the United States, as well as to discuss the impact that each of these events may have had in its resolution. Throughout the history of opioids, we can differentiate ten periods that we went on to describe in this work. In this second part we will evaluate the period between 2010 and the end of 2017.

Period VIII: 2010-2016. FDA announces policy changes. Montreal Declaration. The White House publishes the plan to stop the epidemic. Start of prescription monitoring programs

2010: FDA approves a new formulation of OxyContin and drives new developments (1)

The FDA begins to promote the development of new treatments less susceptible to abuse, safer and more effective for pain management, announces in September the creation of a public-private partnership to carry out several projects under the umbrella of ACTTION *(Analgesic Clinical Trial Translation, Innovations, Opportunities and Networks)* that was established at the University of Rochester.

In October of that year, the shared REMS for all immediate release transmucosal products is launched.

2010: FDA announces policy changes (1)

Among other measures, the FDA launched:

— Re-examination of the risk-benefit paradigm of opioids with an emphasis on public health.
— Increase access and promote the development of anti-abuse formulations *(Abuse Deterrent)*.
— Expert committee meetings before any new application for approval of an *abuse-deterrent* opioid.
— Improve access to naloxone and other treatment options for opioid use disorder *(OAD, opioid abuse disorder)*.
— Inclusion of safety information and warnings in the fact labels and prospects for opioid immediate release formulations.
— Support new alternative forms of pain management.

Currently fewer than 6 *abuse-detterrent* formulations are FDA approved although there are several developments underway.

October 2010: Montreal Declaration IASP (International Association for the Study of Pain): finding that pain management is inadequate in most of the world (2)

In the Montreal statement, representatives of more than 129 countries agreed that the pain was not properly treated in some parts of the world for the following reasons:

— Inadequate access to acute treatment of pain caused by trauma, illness, terminal illness and failure to recognize that chronic pain is a serious health problem that requires management similar to that of other chronic diseases.
— Large deficits in doctors' knowledge of pain regarding pain management and mechanisms.
— Chronic pain is highly stigmatized.
— Many countries have no national policy or have clearly inadequate policies in pain management including an inadequate level of research and education.
— Pain medicine is not recognized as a specialty with a specific knowledge body and defined clinical scope.
— WHO estimates that 5 trillion people live in countries with little or no access to medicines to control moderate-severe pain.
— Strict restrictions on the availability of opioids and other essential medications that are critical in pain management.

Based on that, the Montreal declaration stated that the following rights should be recognized:

1. The right of all people to access pain management without discrimination
2. The right of all people to receive a pain assessment and be informed of ways in which it can be addressed and managed

In the Montreal statement, representatives of more than 129 countries agreed that the pain was not properly treated in some parts of the world

3. The right of every person to have access to adequate pain evaluation and treatment by a medical professional properly trained to do so.

On the basis of these rights, they declared the **following obligations:**

1. Obligation of the government and health institutions to provide necessary health resources to establish laws, policies and systems to help promote access to adequate pain management for people in pain.
2. Obligation of healthcare professionals to offer the patient a competent care in pain management.

2011: The FDA approves Abstral (fentanyl), fourth immediately release transmucosal product (1)

The product is approved with MG and REMS.

The FDA supports the Office of National Drug Control (ONDCP) (1) report published in 2011 containing an action plan to address the national prescription drug abuse epidemic (1,3). Of the 118 pages of the document, only part of a chapter (Chapter 2, principle 2) is dedicated to prescription medication. The title of this section was: *"Curb Pharmaceutical abuse while preserving medical benefits of pharmaceuticals"*. The approach in this section is based on data from two studies *(National Survey on Drug Use and Health NSDUH)* (3,4) showing that 1/3 of those over the age of 12 who first used illicit drugs in 2009 had started this illicit use with a **non-medical use** of prescription drugs. Another study MTF (wider national study on drug use among young people) (3,5) showed that prescription drugs are the second most abused category after marijuana.

The focus of these two studies is on **non-medical use of opioid prescriptions,** but not on the risk of addiction by patients properly treated with opioids for the treatment of their pain. The 2011 MTF study (5) perfectly summarizes the allocation of this **risk to non-medical use of** prescriptions not only in reference to opioids but above all to sedatives, psychotropics and other psychoactive substances. "It seems likely that young people are less concerned about the dangers of using these prescription drugs outside of medical regimen, likely because they are widely used for legitimate purposes".

In both cases, according to the authors, the prescription has been the source of an addiction not in the patient himself but in someone around him. In this sense, it must be clarified that these addictions cannot therefore be attributed to the use of these medicines as painkillers or to the clinical activity of prescribers.

Based on this analysis, the White House published in **April 2011** a plan to curb the epidemic of illicit drug use (not only opioid-related but all psychoactives): *"Prescription Drug Abuse Prevention Plan titled, Epidemic: Responding to America's Prescription Drug Abuse Crisis"*. Today we can access the updated version of this document which will be discussed later (3).

The fundamental objective of this document was to prevent misuse of prescription drugs while ensuring the availability of these drugs for medical use by patients who actually need them. This plan included the establishment of a multidimensional approach: patient education, prescriber education, monitoring systems, medication disposal and implementation strategies.

Data from the NSDUH study: estimated that in 2009, 7 million people over the age of 12 had **made non-medical** use of a prescription in the last month (we recall that it refers to prescriptions for all types of psychoactive drugs not only opioids) and this figure had quadrupled between 1998 and 2008 (4). At the same time, the CDC reported (as the NDCS reports) that prescription opioid-associated deaths had tripled between 1999 and 2006 outweighing heroin and cocaine combinations.

Regarding the 2011 NDCS report (3), discussed above, the report speaks and displays the following alarming figures for **non-medical drug** use between 1998 and 2009: drug-induced deaths per 100,000 population increased from more than 6 to over 13. The number of emergency admissions involving misuse or abuse of pharmaceuticals increased from over 600,000 to near 1.3 million (3).

This data refers to the SAMHSA published in 2010 (6). However, when we look for the primary source of data in the *Highlights of the 2010 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits* report (28) it is seen that within the drug category (with 434.9 emergency visits/100,000 inhabitants in 2010) several types of medicines are grouped:

— Anxiolytic or insomnia medications including benzodiazepines (152.8 emergency visits per 100,000 inhabitants),

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3. *The right to have access to adequate pain evaluation and treatment*

— Antidepressants (34/100,000),
— Opioid analgesics (137.4/100,000).

Emergency visits in 2010 due to non-medical use of opioid drugs were 64% of those related to an analgesic and 31.6% of those related to a medicine, with the group of anxiolytics and treatments for insomnia being the most important (35%) and higher than that associated with opioids (Table I).

As shown in Table I of the same report, emergency visits were mainly associated with oxycodone (43 % of opioids) and hydrocodone (27 % of opioids) and were produced in a population over 21 years of age (6). In any case, it should be considered that the generalization of the problem as raised in the Obama administration document in 2011 concerns the use of all drugs (not just opioids) and refers to a non-medical use. In fact, the most important problem concerns other therapeutic groups such as benzodiazepines, sedatives or hypnotics.

What is undeniable is the increase in opioid-motivated emergency room visits between 2004 and 2010 (6) as the number of oxycodone-related emergencies were 51,418 in 2004 and increased to 182,748 in 2010 with growth rate of 255 % being this drug the mots growing in this period. In any case, benzodiazepines increased from 170 thousand to 408 thousand (+139 %) being therefore a group that should awaken at least the same alarmism as opioid painkillers.

In addition, we cannot know in what percentage of visits the person attending the emergency room is the person who was initially addressed for the prescription and if so, whether the patient followed the dose-frequency-duration guidelines that were prescribed during treatment.

Since this article is based on the historical review of the facts associated with the opioid epidemic in the USA, it is not the subject of this work to analyze in depth all data on the incidence and prevalence of abuse and misuse, which will be the subject of further work.

The Obama administration's 2011 document (3) ends the chapter by talking about ***"SAMHSA is helping train physicians about the importance of proper prescribing practices for opioids, which are routinely prescribed to relieve*** *pain"* without any mention about the other therapeutic groups that, as we have seen, should also be of concern. Based on the OBAMA administration's 2011 report, SAMHSA intended to educate 1,500 physicians in 2011 in at least 8 states.

Table I. Misused and abused drugs most commonly involved in emergency department (ED) visits in the US the year 2010

DRUG	VISITS TO ED PER 100,000 POPULATION	% OF TOTAL PHARMACEUTICALS
TOTAL Pharmaceuticals	**434.9**	**100 %**
Anti-anxiety and insomnia drugs	**152.8**	**35 %**
Benzodiazepines	131.9	30 %
Antidepressants	**34.0**	**8 %**
Pain Relievers	**213.3**	**49 %**
Narcotic Pain Relievers	137.4	32 %
Hydrocodone	37.4	9 %
Oxycodone	59.1	14 %
Non-Narcotic Pain Relievers (by difference)	75.9	17 %

Calculated in base of 6.

One of the most relevant changes that emerged from the OBAMA plan was to promote the implementation in 2010 of the Prescription Monitoring Programs (PDMPs). PDMPs were proposed as a way to combat this misuse and its consequences by using electronic databases of controlled substance requirements, to assist prescribers in identifying potential misuse. 48 states at the time (2011) had authorized the implementation of PDMPs and in 34 it was already in operation. It is important to highlight several points regarding the implementation of this system (3):

— It affected all drugs under control not only to opioids (which in Spain we would understand by psychotropic drugs, including sedatives, hypnotics, ...) however the American administration's information analysis was focused on opioid prescriptions.
— Implementation had to be approved by the governments of each state and each state implemented it autonomously, resulting in variations in the specific agency that controlled the PDMP as well as the type of information that was collected.

The group of anxiolytics represented the 35 % of visits to emergency department due to abuse or misuse of medicines, being superior to the one associated to opioids (32 %)

— The Obama administration document in 2011 directly associated the non-implementation of PDMPs in some states with the high incidence of drug abuse and vice versa regarding the states that had the system *implemented, naming non-participating states "Without PDMPs, a state can become a haven for illegal drug fun and drug-seeking behavior" (3).*
— In 2010, the administration provided funds to assist in the implementation of this system in the states and mobilized several agencies to try to homogenize electronic information that was dumped in each state.

It is surprising that the first alarm signals of the opioid problem are dated 2002-2003 (with increased mortality and deviation from OxyContinTM use to the illegal channel) and took more than 7 years to set up a prescription and dispensing control system. The implementation of this system was also partial and uncoordinated.

In June FDA approved Oxceta (Oxycodone) and Lazanda (transmucosal fentanyl) (1) the latter with MG and REMS. In December it approved OPANA ER (oxymorfona) and in December the shared REMS of oral transmucosal products was launched.

2012: Subsys (sublingual spray fentanyl)

Sublingual spray fentanyl sixth transmucosal oral product, is approved (1).

2012: In May the FDA and NIH (National Institute of Health) (1)

Meet at *the Assessment of analgesic treatment of Chronic pain: A scientific workshop to* review efficacy data available in the use of medicines for the treatment of chronic non-malignant pain.

2012, September: FDA launches 3 projects to examine strategies and interventions regarding their impact on opioid abuse and misuse (1)

— Examine the prescribing habits of doctors who are prescribing opioid in doses greater than an equivalent of 100 mg morphine per day and/or prescribe opioids in combination with benzodiazepines. These identified physicians were targeted by mailings with information and education. The PDMP would examine changes in their prescribing habits.
— Examine different tools **to guide your doctor in prescribing** opioids and reduce opioid misuse, over-use, and abuse. The study targeted 1,300 physicians (1,000 internists and 200 pain specialists, 100 addiction specialists) to determine the knowledge, use and perception of usefulness of these tools:
  - Screening, brief intervention and referral treatment (SBIRT).
  - PDMPs.
  - REMS.
  - Insurers: initiatives.
  - Treatment contracts.

— Estimate the incidence of UDT (urine drug test) for one year after the onset of chronic opioid treatment.

2012, July **FDA approves REMS** for long-release opioid class (1).
2012, Agosto **ACTTION establishes a consortium (CARES)** (1) and the ALERTT project to create a risk classification tool that can be used in clinical and post-marketing studies to identify addiction-related abuse or emergency events.

2013 September, FDA announces a number of measures to increase the safety and appropriate use of long-lasting opioids (1)

Class-wide security warnings and new post-marketing requirements for ER/LA (extended release/Long-acting).

2014 April, FDA approves injectable Naloxone (Evzio) (1)

For emergency treatment of known or suspected opioid overdose. Naloxone quickly reverses the effects of opioid overdose and this product was the first self-injector designed to administer a dose of Naloxone outside the health center.

2014, July FDA approves Targin ER (ER combination of Oxycodone and Naloxone) (1)

It was the second FDA-approved product in the "abuse-deterrent" category.

One of the most relevant changes that emerged from the OBAMA plan was to promote the implementation in 2010 of the Prescription Monitoring Programs (PDMPs)

2014, October, the FDA approves new label for Embeda (morphine-naltrexone ER) (1)

For the treatment of severe pain that requires chronic treatment, daily on an "around-the-clock" (ATC) regimen. This product was the third FDA approved in the "abuse-deterrent" category in the sense that Embeda has properties that were expected to reduce the potential oral or intranasal abuse of the crushed product.

November, the FDA approves Hysingla ER (hydrocodone) ER for severe pain treatment requiring long-lasting ATC daily doses for patients where other treatment alternatives are not appropriate. It was the 4th product approved in the "abuse-deterrent" (AD) category (1).

2015, January: FDA approves modified formulation of Zohydro ER (hydrocodone ER in capsules) (1)

This product did not fall into the AD category.

2015, July: the FDA collaborates with NIDA, CDC, SAMHSA, and HRSA (1)

FDA collaborates with NIDA, CDC, SAMHSA, and HRSA in (1) discussions about incorporating Naloxone into certain health settings (ambulances or settings associated with opioid prescriptions) to reduce the incidence of opioid overdose deaths.

These discussions included defining the population at risk of overdose, such as public health groups being able to work together to use naloxone and reduce the risks of overdose and, at same time, address the legal, regulatory, logistical and clinical aspects related to making naloxone more available.

One of government "star" measures in the United States was the wide distribution and accessibility of naloxone to prevent overdose death. This measure, without going into detail, pretended to reduce mortality, but did not address the root of the problem of legal or illegal opioid misuse or abuse.

2015, August: FDA approves OxyContin (1)

FDA approves OxyContin **for certain pediatric patients for the treatment of severe pain** requiring daily treatment, long-term ATC where other treatment options are not appropriate.

2015, October: FDA approves MorphaBond (ER morphine) (1)

For the treatment of severe pain that requires daily treatment, ATC, long duration. It was the 5th product in the AD category.

2015, November: the FDA approves Narcan (1)

Nasal spray, the first FDA-approved product as "lifesaver" medication that can temporarily stop or reverse the effects of an opioid overdose including heroin. This product quickly expands the availability of naloxone, especially in non-sanitary environments.

Period IX 2016-2018: new legislation at the federal level (Obama and Trump administrations), new FDA actions and new TJC recommendations

2016, February: the FDA replaced the 5 post-marketing requirements (PMRs) published in 2013 with a PMRs with 11 points (1)

Including more detailed measures on how to identify (1) serious risks of misuse, abuse, addiction, overdose and death.

2016, March: FDA announces label changes in immediately release opioids (1)

Among the changes he adds a warning of serious risks of misuse and abuse that can lead to addiction, overdose and death.

2016, April: FDA approves Xtampza ER (oxycodone) for the treatment of severe pain, daily, long-lasting ATC (1)

It was the 6th product in the AD category.

2016, May: FDA approves Probuphine (1)

First buprenorphine implant for the treatment of opioid dependency maintenance. The product releases continuous low doses of buprenorphine for 6 months to be used in patients with

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low-moderate doses of other forms of buprenorphine as part of a complete treatment that includes counseling and psychosocial support.

2016, July: President Barack Obama signed *Comprehensive Addiction and Recovery Act (CARA)* (7)

Contained numerous measures designed to increase the access of PATIENTS (7) with DSU (Substance Use Disorder) to evidence-based care and treatment. None of the 2016 laws (CARA and CARE act of December) significantly changed federal policy and over-dose deaths continued to increase (8).

The CARA Act addressed a chapter dedicated to prevention and education, but mixing 3 types of prevention that need independent approaches:

— Proper pain management: addiction prevention in young people with sports injuries.
— Prevention of overdose mortality: improving access to overdose treatment.
— Prevention of drug crises at the local level.

Concepts that have little in common were mixed and measures as general as crisis management at the local level (proposed in communities) with other specific as trauma in young athletes. However, it did not address the problem in a systematic way according to type of addiction and integrated at the level of the different stakeholders that are relevant in each of the types of addiction.

CARA act included the formation of a task force to analyze, update and communicate guidelines for treating chronic and acute opioid pain. This task force had the mission of addressing a medical and clinical issue but its composition included, in addition to medical representatives and pain specialists, representatives of groups without specific training or clinical experience in pain management such as: mental health treatment experts, addiction treatment experts, patients recovering from ALS (Substance Use Disorder), patients, *pain-related* advocacy groups, veterans' organization and over-dose reversal experts including first responders.

The approach to this action seemed not to go in the right direction for the following reasons:

— It mixed two different problems (prescription addiction versus addiction from illegal opioid use) and attempted to obtain a single solution by addressing both problems at the same time.
— Writing clinical guidelines for opioid use in pain treatment is a task to be done based on the evidence and experience of pain experts and other prescribers, as well as likely incorporating patients with pain of different types at the end of the process.
— Pain treatment guidelines have no relevance in addictions to illegal opioids and have little to do with taking into account the opinion of people with addiction and recovery
— The opinion of patients who have suffered or suffer from opioid addiction is relevant for analyzing other phases of an action plan, but not for determining or reviewing clinical pain treatment guidelines.

The other chapters of the CARA Act were devoted to other aspects that have changed the address of the problem in the United States:

— Law enforcing and treatment: passing some responsibility for acute overdose treatment to security forces.
— Treatment and recovery: mixing the treatment of addiction to prescription opioids with addiction to illegal drugs (as heroin), building recovery homes.
— Treatment services for women, families and veterans.
— Encouraging initiatives to address opioid prescription abuse.

These laws did not have the expected impact. The definition of the problem was wrong from the beginning of the crisis and this error has been dragged along all legislative and executive measures. As the definition of the problem was wrong, the approach and action plans put in place could not be effective. In addition, the legislative focus is on the consequences and not on the causes. Finally, the legislation at the state level has been different and has been applied or unevenly.

Although the overall approach is wrong, there are positive aspects in the CARA act such as strengthening the implementation and coordination of data collected by the Electronic Prescription Control System (PDMPs), which is, undoubtedly, one of the most

None of the 2016 laws (CARA and CARE act of December) significantly changed federal policy and over-dose deaths continued to increase

effective measures to control the non-medical use of a prescription and to prevent the abuse of a patient in medical treatment with opioids.

2016, August: FDA approves Troxyca ER (oxycodone and naltrexone ER) (1)

FDA approves for the treatment of daily severe pain, long-lasting ATC. It was the 7th product in the AD category.

2016, August: the FDA announces class changes in data labels (1)

FDA announces class changes in data labels to help inform prescribers and patients about the serious risks associated with the combined use of some opioids and benzodiazepines.

2016, December: President Barack Obama signed the *21st Century Cures Act (9)*

This law included a budget to fund innovation projects in response to opioid abuse as $1 billion to fund states in addressing the opioid abuse crisis (e.g. PDMP, abuse prevention, training of opioid prescription and abuse prevention health professionals, federal DSU treatment services). In this law the word "opioid" is mentioned only in 6 pages out of a total of 312 which gives an idea of how irrelevant this particular issue was within law.

2016, December: the FDA publishes a number of safety changes (1)

FDA publishes a number of safety changes in the product labels of various product classes (immediate release opioids, methadone, buprenorphine) in relation to serious safety risks as well as the risk of combination with benzodiazepines.

2017, January: FDA approves Arymo ER (mofrina ER) and Vantrela ER (hydrocodone ER) (1)

F8th and 9th products approved as AD (abuse deterrent).

2017, April: the FDA restricts the use of codeine and tramadol in children (1)

FDA restricts the use of codeine and tramadol in children due to high risk at respiratory level or even death, especially in children under 12 years of age. Its use in children under 12 years of age was prohibited and limited in the elderly.

2017, April: FDA approves RoxyBond (oxycodone) (1)

The first FDA-approved immediately release product that describes AD properties in consistency with FDA guidelines for 2015. The studies presented showed that RoxyBond had tablets resistant to certain forms of manipulation such as crushing, grinding avoiding the extraction of oxycodone from the tablet with the aim of its use for non-medical uses in the illegal circuit.

2017, Mayo: the FDA published "FDA education blueprint for health care providers involved in the management or support of patients with pain" (1)

Included information on pain management, principles of acute and chronic pain treatment, and non-pharmacological and pharmacological treatment with both opioid and non-opioid.

Up to that point, all measures submitted by the FDA in 2015 to 2017 had focused on the following 3 aspects of the problem:

— Warning of the risk of misuse and addiction in fact labels and leaflets.
— Avoid manipulation of prescription medicine ant its use for non-medical, illicit purposes.
— Reduce mortality by immediately availability of Naloxone.

The FDA's "education blueprint" document was much-needed, relevant and refocused but late. This training for opioid prescribers should have been facilitated and standardized much earlier, although is true that sources of training and professional information about the good use of opioids were available to any physician through clinical guidelines and medical societies. For example, in Europe, the European Pain Federation (EPF) published a very comprehensive "position paper" in 2017 about the appropriate use of opioids in chronic pain management (10).

Although the overall approach is wrong, there are positive aspects in the CARA act such as strengthening the implementation and coordination of data collected by the Electronic Prescription Control System, which is, undoubtedly, one of the most effective measures to control the non-medical use of a prescription and to prevent the abuse of a patient in medical treatment with opioids

2017, June: FDA asks Endo Pharmaceuticals to withdraw the Opana ER (oxycodone)

FDA asks Endo Pharmaceuticals to withdraw the Opana ER (oxycodone) from the market on the basis that the benefits of the product may not remain higher than the risks at that time. Endo ends up announcing the withdrawal of this product voluntarily in July of that same year.

2017, September: the FDA sends letters to opioid manufacturers of immediate (1)

Release products informing them that their products must undergo the same REMS requirements as ER opioids.

2017, October: the American government

The American government officially declares the opioid epidemic a public health emergency (11).

2017, November: FDA approves Sublocade (1)

First monthly injectable of buprenorphine for the treatment of moderate-severe opioid abuse in adult patients who have initiated transmucosal buprenorphine treatment and who have been in stable doses of buprenorphine for at least 7 days.

2017: THE NASEM Consensus report (12)

National Academies of Sciences, Engineering and Medicine is published, a report on the current state of science regarding the abuse and misuse of prescription opioids and the role of these drugs in the treatment of pain. Although the FDA had requested analysis in relation only to prescription opioids, the study commission considered that due to "the high interrelationship between prescription opioids and illicit drugs", it was necessary to refer to both areas.

"The committee interpreted its charge as focusing primarily on prescribed opioids, although its analysis of the epidemiology of the opioid epidemic and strategies for addressing it took into account the diversion of prescription opioids illicit into markets and the impact of use of prescription opioids on use of illicit opioids, such as heroin."

The report relies on some publications and studies to quantify the non-medical use of opioids in 1.8 Million new users in 2012 (including illicit uses). The report also quantifies that 80 % of heroin addicts began their addiction through prescription opioids, based on a Muhuri et al. 2013 study (13). Muhuri's study analyzed the switch from non-medical *prescription pain reliever (NMPR)* to the use of other illicit drugs and therefore analyzes the move from one illicit use to another, but not the passage of patients who had a medical use of opioid to illicit use, which was not quantified in this study. In addition, the Muhuri study was based on asking the affected ones themselves, so the reliability of the answers can be questioned. The same authors of this study admit that the theory of passage of prescription opioids to *illicit use "the Gateway theory" can* be defended as an existing risk for a certain volume of chronically treated patients at high doses when other risk factors are associated, but most patients with opioid medical treatment are not at risk and **"An overwhelming majority of people who use prescription opioids do not continue to use them chronically and so are not at risk for switching to using heroin".** They further identify that concomitant use of benzodiazepines is a factor with a great impact on the over-dose ratio and details that "***The*** vast majority of patients prescribed opioids do not have mal-use of the drug. However, the effects associated with opioids could make that end users of these prescriptions may not be those initially intended."

The FDA's "education blueprint" document was much-needed, relevant and refocused but late

"The Gateway theory" can be defended as an existing risk for a certain volume of chronically treated patients at high doses when other risk factors are associated, but most patients with opioid medical treatment are not at risk

REFERENCES

1. FDA. FDA.gov [Internet]; 2019 [cited en febrero de 2019]. Disponible en: ***https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM566985.pdf***.
2. Declaration of Montreal. IASP-PAIN.ORG [Internet]; 2010 [citada en febrero de 2019]. Disponible en: ***https://www.iasp-pain.org/DeclarationofMontreal***.
3. 2011 NDCS [Internet]; 2011 [citada en noviembre de 2018]. Disponible en: ***https://obamawhitehouse.archives.gov/sites/default/files/ondcp/ndcs2011.pdf***.
4. SAMHSA. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. Rockville MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586 Findings; 2010.

5. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future. [Internet]; 2011 [citado en febrero de 2019]. Disponible en: *http://monitoringthefuture.org/pubs/monographs/mtf-overview2011.pdf*.
6. SAMSHA. SAMSHA-DAWN. [Internet]; 2011 [c itado en febrero de 2019]. Disponible en: *https://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.htm*.
7. America CUSo. congress.gov. [Internet]. [citado en febrero de 2019]. Disponible en: *https://www.congress.gov/bill/114th-congress/senate-bill/524*.
8. Davis CS. The SUPPORT for Patients and Communities Act—What Will It Mean for the Opioid-Overdose Crisis? N Engl J Med. 2019;380(1):3-5. DOI: 10.1056/NEJMp1813961.
9. 114th Congress. 21st Century Cures Act. Public Law 114-255. DEC. 13, 2016 130 STAT. 1033.
10. O'Brien TO, Christrup LL, Drewes AM, Fallon MT, Kress HG, McQuay HJ, et al. European Pain Federation Position paper on appropriate opioid use in chronic pain management. Eur J pain. 2017;21(1):3-19. DOI: 10.1002/ejp.970.
11. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. Pain Ther. 2018;7(1):13-21. DOI: 10.1007/s40122-018-0097-6.
12. The National Academies of Sciences, Engineering and Medicine. Pain management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of prescription opioid use. Washington, DC:, The National Academies Press; 2017.
13. Muhuri PK GJDC. Associations of Nonmedical Pain Reliever Use and Initiation of Heroin use in the United States. CBHSQ Data Review. Rockville MD: SAMSHA, Center for behavioral health statistics and quality; 2013.