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SPECIAL ARTICLE

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

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

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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. This article corresponds to the third and final part of our analysis. We continue with the study of federal legislation implemented by government administrations in the United States to end events held until the end of 2019.

RESUMEN:

En este trabajo se realiza una revisión de los hechos históricos más relevantes ocurridos en Estados Unidos con relación al 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. Este artículo corresponde a la tercera y última parte de nuestro análisis. Continuamos con el estudio de la legislación federal implementada por las administraciones gubernamentales en Estados Unidos para finalizar con los eventos producidos hasta finales del año 2019.

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 third part we will see the events between end of 2017 and 2019.

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

The NASEM document (1) quantifies that the mean OUD (Opioid Use Disorder) ratio is 8 % of patients prescribed opioids, and the combined ratio of OUD/mal-use/aberrant behaviors is between 15 % and 26 %.

The main strategies proposed in document NASEM 2017 (1) to address the opium epidemic were the following:

1. **Restrict access:** improve access to drug take-back programs: withdrawal of medicine to the pharmacy (which would be equivalent to the SIGRE program in Spain)
2. **Influence prescribing practices:**
   - Establish educational and curricular pain materials for healthcare providers in medical schools and other health professionals.
   - Facilitate reimbursement of pain treatments including pharmacological and non-pharmacological treatment.
   - Improve the use of PMPDs for monitoring and intervention.
3. **Reduce demand:**
   - Assess the impact of patient and public education on opioids by promoting safe and effective pain treatment.
   - Expanding OUD treatment.
   - Improving education on OUD treatment among health professionals.
   - Remove barriers to coverage of medicines approved for the treatment of OUD.
4. **Reduce damage:**
   - Encouraging prescribers and pharmacists to assist in the approach of the OUD.
   - Improve access to Naloxone and safe injection equipment (prevent dead and infections).

November 2017: Trump administration releases "The president's commission on combating drug addiction and the opioid crisis" (2)

This paper raises the current opioid epidemic as the second in the history of United States, and re-encompasses both prescription opioids and illicit opioids in the crisis. This diagnostic error continues to be maintained throughout the government's management of the epidemic in the United States. The document discusses several factors that have developed or promoted the current opioid epidemic, all related to illegal use except one (point 4):

1. Production and distribution of purer, more powerful, oral and addictive opioids
2. Generalization of the availability of cheap illicit heroin
3. Influx of highly potent fentanyl and fentanyl analogues
4. Transitioning opioid prescription abusers to heroin and fentanyl use
5. Production of illicit opioid pills with deadly fentanyl forms or formats
6. Fentanyl use affects a wide age range, economic status, both rural and non-rural areas, all races and religions.

The Trump administration document lists the following factors as contributors to the crisis, all directly related to prescription drugs:

— ***Unsubstantiated*** claims: mentioning the 1980 NEJM letter to the publisher about the low addictive potential of opioid painkillers as well as Portenoy's study that the document defines as "problematic" (3,4) and accuses these two publications of the erosion of historical evidence on iatrogenic addiction and aversion to opioids with *"low-quality evidence that was accepted by federal agencies".*

The main strategies of NASEM to face the opioid epidemic were restrict the access, influence the prescribing practices reduce the demand and reduce the damage

- ***Pain patient*** advocacy: Patients and some doctors are accused of promoting pain management using opioids. Tools such as diagnosing pain, measuring patient satisfaction... are accused of contributing to the opioid epidemic.
- ***The opioid pharmaceutical manufacturing and supply chain industry: the pharmaceutical industry is directly accused of relying on*** specific facts that may in themselves be criticized, but extrapolated (they mention for example training events to 20,000 doctors talking about low addictive potential, aggressive promotion of oxycodone between 1997-2002 associated with a 10-time increase in prescriptions for treating moderate-severe pain, ER formulations that were adulterated for illicit use). While we may understand that some of these industry actions may have contributed negatively to the increase or excessive use of certain opioids, it is not accurate to associate this fact with the increase in the use of illicit opioids or the use of legal opioids in an illegal circuit.
- ***Rogue pharmacies and unethical physician prescribing:*** the distribution channel is also accused of unrestricted, unethical use causing non-medical use of many prescriptions. Again, the analysis does not provide an objective sizing of these accusations and again refers to an illegal use of legal channel product.
- ***Pain as the 5th vital sign:*** this is another of the "mantras" they use in various means to blame the medical environment for the crisis. It has already been explained above what is the pain as 5th vital sign (5,6) and what positive impact it had in pain management. However, this historical fact is repeatedly used as a starting point for increasing opioid prescriptions that resulted in the current epidemic in the United States. The TJC, as we have seen, has been forced to repeatedly clarify its position in this regard and the Trump administration anticipates, in its 2017 document, that TJC will eliminate the requirement to measure pain in all patients.
- ***Inadequate oversight by the Food and Drug Administration (FDA): At this point Trump administration directly attacks and*** holds the FDA accountable as an agency responsible for ensuring the health, efficacy and safety protection of human-use drugs. "The *FDA has conducted inadequate oversight even when deaths accumulated and when there was a clear lack of evidence on the safety of chronic use".*
- According to the American administration document, the FDA has had the following responsibilities in the current epidemic: It accepted claims of new opioids re-formulated as non-addictive, It did not improve clinical studies of insufficient duration to detect addiction, lack of rigorous post-approval programs to monitor adverse effects such as addiction, failed in quantifying the risks associated with deliberate use for fun, illicit misuse of opioids, risks that outweighed benefits in patients, accepted industry claims that iatrogenic addiction is very rare and that delayed absorption of OxyContin reduced abuse.
- ***Reimbursement of prescription opioids by*** insurers: opioid prescriptions multiplied by 4 between 1999 and 2014.
- ***Poor medical*** education: regarding pain management, opioid prescribing, screening and addiction treatment.
- ***Lack of education for patients and family members regarding the risks of addiction and overdose.***
- ***Quality and satisfaction ratios to physicians:*** pressure on physicians by patients, by the requirements to meet the 5th vital sign or reimbursement metrics.
- ***Lack of long-term*** vision: limitations and barriers to use (abuse-deterrent, prescription control) have led to a lowering of the illicit opioid market, resulting in a transition from prescription opioid to illicit opioid.
- ***Insufficient treatment services to meet the demand for treatment (medication-assisted treatment MAT).***
- ***Lack of prevention strategies at the national level.***

Trump administration directly acuses, among others, doctor, patients, FDA, pharmacies, V vital sign, insurance companies

2018, January: FDA announces safety changes in cough and cold medications containing codeine or hydrocodone (7)

Limits their use to adult patients due to risks and adds safety notices in labels regarding the risk of abuse, addiction, overdose, death or respiratory distress.

2018, January, the FDA conducts a public session "Opioid Policy Steering Committee Prescribing Intervention- Exploring a Strategy for implementation" to (7)

Receive *the inputs* of different stakeholders on how the FDA should (under its REMS authority) improve the safety of the use of analgesic opioids by reducing over-prescribing in order to reduce the incidence of new addictions and limit the misuse and abuse of these painkillers.

This action goes back in the right direction, looking for the correct prescription of opioid as a key point of preventing a potential medical misuse or addiction. Again, we believe that this should have been one of the first measures taken by FDA in the early 2000s. However, it arrived in 2018!

2018, in February: the FDA discusses hydexor (7)

Approval (fixed combination of hydrocodone, acetaminophen and prometazine) for the short-term treatment of severe acute pain required by opioids while preventing and reducing opioid-associated nausea-vomiting.

2018, April: FDA hosts (7). The meeting "Patient-focused drug development for Opioid Use Disorder (OUD)" in collaboration with NIDA

Among other activities, the FDA is promoting patient and community counseling programs to engage individuals with OUD.

2018, April: FDA draft on opioid dependence: development of buprenorphine depot for (7) treatment

This document refers to the key points of the FDA's position regarding drug development and relevant clinical studies for analyzing products with buprenophrine depot.

2018, May: FDA approves Lucemyra (lofexidine) first (7)

Non-opioid treatment for withdrawal syndrome associated with abrupt opioid discontinuation.

2018, May: the FDA discusses the application of sublingual buprenorphine spray (INSYS) (7)

FDA discusses the application of sublingual buprenorphine spray for moderate-severe pain treatment that requires opioids.

2018, July: FDA approves the first generic Suboxone sublingual film

Discusses the application of ER oxycodone in capsules.

2018, August: FDA analyzes the results of TIRF-REMS (transmucosal immediate release fentanyl medicines risk evaluation and mitigation strategy) (7)

This program launched in December 2011 required

- TIRF prescribers for outpatient use were certified.
- Pharmacies that dispense these drugs for both intra-extra hospital use were also certified.
- Fulfill doctor-patient forms prior to dispensing for outpatient use.

Again, a measure in the right direction, but in our view late and too bureaucratic.

2018, october: Trump signed the SUPPORT for Patients and Communities Act (8)

This 250-page law recently to promote a coordinated federal strategy to address the epidemic. The law includes measures at the level of medical care of patients with DSD (Medicare, Medicaid primarily in relation to the treatment of DSU), measures to strengthen logistics control, dispensing and withdrawal of controlled substances (FDA) as well as measures to improve the control of opioid prescriptions both intra and extra-hospital.

Although this law is based on the same basic error already discussed above, it is true that it is more positive for the prevention of incorrect opioid prescriptions, especially in addressing 3 fundamental aspects that go in the right direction:

- Improve prescription control and prescription data collection at the extra-hospital level.
- Improve the application of treatment guidelines at the intra-hospital level, especially in post-surgery.

FDA promotes patient and community counseling programs to engage individuals with OUD

— Avoid any financial incentives in Medicare or Medicaid reimbursement plans that may result in an economic benefit to your doctor from prescribing an opioid versus other analgesia options.

It is important to note here that none of these measures would be necessary today in Spain where from the first moment a detailed prescription control is carried out, there are very detailed guides to the use of opioids in post-surgery and there is no economic incentive for the doctor to prescribe an opioid or not versus other alternatives.

2018: TJC Standards in Pain Management (5)

Standards recently published by TJC address the pharmacological management of pain and opioid use in terms of organization and policies to improve the safe use and prescribing of opioids. The new 2017 standards recommended:

— Establish pain assessment including psychosocial risk factors that can affect the patient's self-assessment of pain.
— Include patients in the development of their treatment plan and generate realistic expectations and goals.
— Focus on assessing how pain affects physical function.
— Monitor opioid prescription profiles.
— Promoting access to non-pharmacological pain treatments.
— Promote safe use in the hospital and outside the hospital to prevent misuse through measures such as:
  • Identification of high-risk patients
  • Having equipment to monitor high-risk patients
  • Make it easier for physicians to access prescription monitoring program (PDMP) databases and promote their use before prescribing opioids.
  • Educate patients and family members on the safe use, storage and elimination of opioids.

September 2018: FDA takes new steps to drive the appropriate and rational use of opioid prescriptions (9)

One of the measures is the approval of the new REMS plan to improve the communication of serious risks associated with opioid use in pain patients by healthcare professionals. This REMS includes for the first-time immediate release drugs for out-of-hospital use as well as ER-LA formulations that had already been included in the 2012 REMS. The goal is to prevent addiction in patients with opioid prescriptions, especially avoid unnecessary or inappropriate prescribing of opioids and promote a more rational prescription. The modification of the REMS system passed from including 62 products to include 347 opioid products for out-of-hospital use. Other developments were:

— Need training for healthcare professionals involved in pain management, not just prescribers (e.g. nurses and pharmacists). This training should also cover broader areas regarding pain management (alternatives to opioids)
— Approval of new product labels including training for health professionals
— Notification of the development of evidence-based prescription guidelines, specific by indication to assist in prescribing opioids.
— Demonstrate the need for greater knowledge of pain and how to manage pain patients, considering all pain management options (pharmacological and non-pharmacological) and reserve opioids for cases where the other options are not appropriate or when the benefits out are greater than the risks.
— Detail recommendations for managing the patient in opioid treatment: initiation of treatment, continuous monitoring of the patient and how to identify signs and symptoms of abuse, revision of the PDMP system, long-term management (changes in base disease, opioid changes, adherence monitoring and identification of signs of abuse), how to recognize and act on a situation of abuse, when consulting with a pain specialist and how to discontinue an opioid.

The same FDA acknowledges that:

— There is no mandatory federal requirement for healthcare professionals (HCPs) regarding taking REMS training and completing this training is not a precondition for prescribing opioids to patients.

TJC published in 2017 the standards of pharmacological management of pain and opioide use, proposing, for instance, include psychological risk factorsin patient's evaluation, identification of high-risk patients, have equipment to monitor those patients and promote the access to PDMP data

— And they include immediate consequences of non-treatment or under-treatment of pain: reduce quality of life, functional and physical disability, high economic costs. Chronic pain is also associated with fear, anger, depression, anxiety, reduced ability to develop normal and professional activity. "It is critically important that HCPs have all the information they need to properly treat their patients and safetly manage their pain. It is also critical for HCPs to understand when opioid analgesics are the appropriate treatment and how to implement best practices to ensure their patients' safety".

is important to note that the FDA itself denounces the lack of unified policies at the federal level and the same accreditation system is not mandatory by doctors. Lack of training among some professionals with the ability to prescribe opioids is a part of the problem, but not the most relevant and there is a fundamental difference in the prescribing profile of U.S. opioids relative to Europe and Spain as one of the most prescribed opioid professionals in the United States is the dentist or physical therapist-rehabilitator.

Late 2018: new era of opiophobia and "hostility" to chronic opioid patient in the american health system

At the end of 2018 we can clearly detect a new era of opiophobia in the United States and a climate of polarization regarding opioid use in that country (10,11).

Some authors already talk about the consequences of repeated exposure to certain types of information: the perceptions of doctors are conditioned, and these perceptions are transformed into assumptions that in turn condition clinical decisions. The current assumptions about prescribing opioids have not been scrutinized (12,13).

Base clinical habits in certain perceptions or assumptions are causing doctors to change their opioid prescribing patterns fundamentally by increasing the use of sub-analgesic doses and eliminating their use in many patients or even completely rejecting their use (10). It is therefore relevant to offer facts and data confronted with perceptions and opinions (10).

opiophobia in the United States, along with the measures implemented in recent years, may be criminalizing the chronic patient in opioid treatment by making him a "suspect" to be monitored.

2019, January: Some authors are calling for an integrated federal solution

"More than a decade after the crisis began in the United States, an integrated solution has not yet been put in place at the federal level to reduce over-dose, mortality and disability rates" (8).

Final discussion

The first opioid crisis, as explained above, was largely associated with the prescriber's ignorance about the addictive potency of the drugs used at the time and the trivialization of their use as a result of this mistrust. The solution to this first crisis was the control and education of prescribers.

This new epidemic is different from that first one and yet American agencies and government have considered that, again, the main source of the problem was the indiscriminate medical use of opioids. As we have already seen in this historical vision, the current opioid crisis in the United States has two components with different dynamics (medical use and illicit drugs use) that cannot be mixed. The 2017 Trump administration document did not differentiate these two components and dragged this error, so the recommended measures are in many cases inefficient (2).

It is therefore essential to point out that in the current opioid epidemic in the United States the participation of prescription opioids is marginal and not central, with illicit drugs accumulating most of the morbidity. Data published by Wu L. Et al in 2017 show this (data from 2,000 patients recruited between 2014-2015 in 5 U.S. centers): Out of total participants a 76 % provided data on the use of various substances in the last 12 months 4.9 % of them used prescription opioids and 36 % of the sample met Substance Use Disorder (SUD) criteria (14). The sum of the prevalence of DUD (Drug *Use Disorder)* was 30 % for illegal substances (marijuana, cocaine, heroin, illegal opioids, etc.) versus only 2.4 % for prescription opioids and 1.4 % for prescription sedatives (the total sum

FDA itself denounces the lackof unified policies at federal level

associated with prescription medicines wase 3.5 %). The size of SUD associated with illegal drugs is 12.5 times that the one associated with prescription opioids. Comparing only Cocaine + Heroin + Illegal Opioids (12.9 %) versus prescription opioids (2.4%) the weight difference is still very relevant: 5.4 times higher (Figure 1) (14).

It is therefore fair to say that the most important part of the opioid problem falls on illegal substances and that a small part of the problem is undoubtedly associated with prescription opioids, but it seems clear that under no circumstances has the prescription been the source or main cause of the current epidemic in the United States. It is therefore basic and essential to analyze separately both areas (illegal opioids and prescription opioids) as they are two completely different realities where channels, usage impulses, user profiles, origin of use and consumption, suppliers, products used, etc... are diametrically different. These are therefore different problems that need to be studied and addressed with different measures.

It is true that between these two areas there may be an overlapping area and that some patients treated with prescription opioid for their pain may have switched to illegal consumption, but this intersection is small (14) and cannot explain or justify the numbers of ODS, overdose and mortality seen in the United States.

With regard to the guilty identified by the U.S. governments: Porter and Jick's 1983 study is relevant in terms of the number of patients studied, although it is true that it was a population of hospitalized patients and that it is not specified whether or not they are cancer patients. Regarding Portenoy's publication, it should be noted that the author detailed very specific recommendations on how to make a correct prescription and monitoring for an opioid. These recommendations remain valid today and in fact several of them are part of the subsequent recommendations documents that have been drafted in the USA and Europe to address the opioid crisis (12). Clearly, many of these recommendations from Portenoy et al. (4) have not been implemented in American clinical practice which may have contributed to an increase in mal-prescription and misuse of opioids, understanding by mal-prescription the one that: does not evaluate pain properly, does not make several previous control attempts with non-opioids, does not associate other therapies with the opioid, does not evaluate the psychological risks of the patient, does not evaluate the need properly, do not perform a good dose titration and do not carry out a monthly monitoring plan of the patient or limit the patient's mediation to 1 month of treatment. If all these initial recommendations of Portenoy et al. had been observed, history would certainly have been different in the United States.

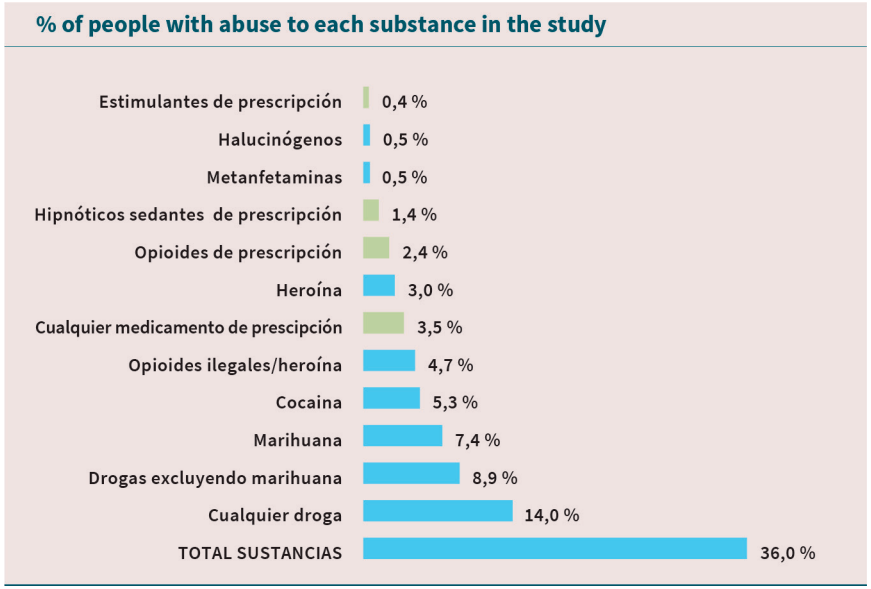

Figure 1. % of people with abuse to each substance in base of Wu et al study (40). Blue: illegal substances. In green the prescription drugs.

On the other hand, the prescription mechanisms for narcotic drugs implemented since the 19th century in Spain and Europe have achieved a higher level of control and monitoring of patients on opioid treatment (15).

Zenz et al. in 1993 (15) revealed a dual situation: on the one hand, the increase in opioid addictions (mostly illegal ones) that was not correlated with the level of prescription opioids and secondly the under-treatment of severe pain in cancer patients. Zenz et al.'s fundamental goal in 1993 (15) was to demonstrate that in Europe one million cancer patients were in pain and unsatisfactorily treated and therefore it was necessary to make prescription opioids more available to cancer patients.

Some authors or institutions (2) have also blamed Zenz, Porter or Portenoy for boosting opioid prescribing in Europe and the Uni-

Many recommendations of Portenoy have not been implemented in American clinical practice which may have contributed to an increase in mal-prescription

ted States. The under-treatment of the 1990s was causing suffering to many patients who did not get adequate pain relief and pain experts were needed to put on the table the need to use available resources (including opioids) to manage this pain, as already recommended by WHO. The recommendations of the Brussels conference (15) or those of Portenoy et al. (4) provided clear guidelines for good use of painkillers and combined in a very balanced way the need to provide pain relief with the need to control possible adverse effects (including abuse) however, criticism to these authors often obviates these recommendations.

Some authors (11) have also tried to accuse TJC alongside Porter, Zenz or Portenoy of being promoters of the epidemic in the United States, but all of them highlighted the need to follow a number of clinical practice recommendations before and during opioid prescribing. How many doctors and centers in the United States followed these recommendations?

Recent critics to TJC by some doctors and authors has led to the TJC explaining its 2001 publication. The TJC has stated that neither in the 2001 document nor currently does the TJC consider pain to be the 5th vital sign and that at no time has this concept been part of (5) clarifying that its sole objective is to ensure that accreditation processes focus on achieving high-quality systems but at no time was the promotion of use of painkillers.

From our point of view, the TJC only proposed the implementation of processes and policies to evaluate, quantify and identify pain in hospital patients in order to be able to perform a correct treatment and follow-up of this pain with the aim of reducing the adverse effects of persistent pain both physically and psychologically.

In this sense, the work of TJC was absolutely necessary and essential and promoted the treatment of pain and the specialization in pain that has benefited thousands of patients since then. In addition, TJC also promoted the correct evaluation of pain, which is a fundamental aspect to achieve good use of the opioid (dose, duration, patient profile and appropriate indication) as already required by Portenoy and Zenz in the late twentieth century.

Another contributing factor to increased opioid use in the United States has undoubtedly been the malpractice of some pharmaceutical laboratories. However, we cannot fall into the unfair generalization of this accusation. The FDA quickly identified the problem with Purdue Pharma and initiated immediate action, which was not necessary with any other pharmaceutical company. As we have mentioned, OxyContin's increase in prescription was largely caused by the transfer of use to the illicit channel as well as not following the recommendations that Portenoy and Zenz once gave on how to address the good use of opioids in prescription.

So far, four factors that contributed to the gestation of the epidemic in the USA were:

— Lack of regulation and control of prescription and dispensing: diversion of use to the illegal segment. Neither the product was consumed by the patient prescribed, nor was it used in the prescribed dose-duration-indication, but was adulterated for use in different form and route of administration. It is also important to note that although OxyContin deviation was already detected in 2002-2003, prescription and dispensing control (PDMPs) measures were not implemented until 2010. These two facts are key factors that have increased the problem in the United States:
  - Lack of opioid prescription and dispensing control and regulation systems
  - Delay in the implementation of such control and regulation systems.
  - It is therefore obvious that in the field of prescription there have been serious deficiencies in the medical control and misuse systems of prescriptions that have motivated that 2.4 % of prescription opioid addictions that we saw above.
— Lack of adequate training in relation to the patient profile and adequate indication in which to use the product. In this case the FDA acted by adding and detailing in some way these points, but in an insufficiently concrete way.
— Purdue Pharma misleadingly promoted the product and was convicted of it in 2007.
— In the USA, measures such as PDMPs (3) have had to be implemented by state and not all states have implemented it, and those that have implemented it have not done so in the same way. In addition, prescription and dispensation data are not fully centralized or shared across all states. Here we find a fundamental difference with the control system in Europe and Spain.

An in depth analysis is lacking to answer some questions, as quantify what part of the problem is associated with medical use and which one correspond to no-medical use of prescription opioids

In short, an in-depth analysis is lacking to answer the following questions:

1. What part of the problem is associated with medical use and non-medical use? and within medical use, how many prescriptions had been made following the recommendations of Portenoy, Zenz, TJC and the FDA? This analysis could clarify where opioid medical use failures occurred: pre-evaluation of the patient, previous treatments with other painkillers, adequate knowledge of pain mechanisms and types, dosing and treatment guidelines, frequent patient follow-up and monitoring...
2. Of the people who went to the emergency room for over-dose problem or prescription opioid misuse, how many were the patients who had had their prescriptions?
3. How many of them had followed the prescription guidelines prescribed by the doctor?
4. How many of them had been adequately monitored for opioid prescribing (monthly)?
5. How many of them had the prescription been performed correctly with a pre-evaluation of the indication, failure prior to other painkillers, dose-duration and frequency and adequacy of the patient profile? If we recall the recommendations already made by Portenoy (4) and Zenz (15) in the late 20th century, it could be said that many of the CJJ's recommendations were already provided for in its publications.

Measures taken by American agencies and governments have generated a new opiophobia that is creating a climate of "blocking access to control of pain, stigma and hostility in the health system" (10). A clinical case has already been published that reflects this hostility and stigmatization or criminalization of the patient in opioid treatment (11) where the rigidity of the American system is evident and how this rigidity is causing patients perfectly controlled with opium for years to go to illicit use when abruptly expelled from the medical system to treat their chronic pain.

The measures taken have been ineffective in reducing the mortality or incidence of overdose in the United States, as we have seen, the problem of medical prescription and illegal use of opioids are two distinct problems that need to be addressed in completely different ways. Rose (10) in his magnificent 2018 review concludes that *"the recent upsurge in opioid-related deaths is attributable to the illicit opioids fentanyl and heroin. This pattern of over- dose fatality is unlikely to respond to regulation of access to medically prescribed opioid analgesic"*.

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A new opiophobia is creating a climate of blocking access to control pain, stigma and hostility in the health system

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