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SPECIAL ARTICLE

Historical analysis of opiods epidemic in United States of America (Part I)

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

AUTHORS:

Esperanza Regueras Escudero, José López Guzmán
Universidad de Navarra

CORRESPONDENCE:

Esperanza Regueras Escudero
eregueras@unav.es

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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. The analysis has been divided into three parts for publication. In this first part we analyze the most relevant events that happened between 1800 and 2009.

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. El análisis ha sido dividido en tres partes para su publicación. En esta primera parte analizamos los acontecimientos más relevantes acontecidos entre el año 1800 y el año 2009.

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.

Period I: change in the perception of pain and first opioids. Pain as pathology

Before the year 1800 pain was considered an event, phenomenon or existential experience associated with aging and as such was accepted. Despite being the oldest medical problem, his physiopathology has recently begun to be known (1). Before the 19th century pain was seen as a sign of a patient's viability and energy, a measure of the effectiveness of a treatment or associated with a religious or philosophical meaning. From the early 19th century onwards, the importance of the individual's experience was highlighted and the attitude towards pain began to change, manifesting itself first in the use of anesthetics for surgery, proposed by T. G. Morton or James Young Simpson in 1848 (2). The introduction of anesthesia was one of the great milestones of modern medicine and at the time generated a great debate in both Europe and the United States, around, for example, the idea that sedation during surgery could delay the healing process. Most surgeons however quickly welcomed the possibility of longer and more complex surgeries thanks to anesthesia, but even until the mid-19th century its use was not universal. Morphine industrial manufacturing began in Germany around 1820 and in the United States a decade later (3). Opium-based products that were available in liquid forms, pills and powder proliferated thereafter. These products were unregulated and marketed as over-the-counter formulations for self-medication (1).

Period II: first opioid epidemic

Around 1870 doctors expressed concern about the "habit of morphine" or "narcomania" (4). In 1898 Bayer introduced a new cough treatment called Heroin (diacetyl morphine). Early reports said that this drug had less addictive potential than morphine, in 1910 in the United States there was the first major epidemic of opioids and illicit use of this drug on the street (crushing and concentrating tablets). Its use spread so much that the medical profession supported the Harrison Narcotic Control Act approved in 1914 (1).

Period III: opiophobia 1915-1970

Regulations associated with the *Harrison Act* and enacted by the American Treasury Department in 1915 indicated that keeping addicts in narcotic treatment to prevent withdrawal syndrome was not a legitimate medical practice. The federal government began using this Act to prosecute physicians who issued prescriptions for that purpose, and in1919 the U.S. Supreme Court upheld this legal interpretation of the federal government (5).

The *Harrison Narcotic Control Act* had a major impact on doctors and patients of the time who preferred to avoid opioid use as much as possible (6). Cancer patients were then encouraged to refrain from taking opioids until their lives could be "counted in weeks" (7). The use of morphine was highly regulated and its prolonged administration was approved only for dying patients (1).

As a result of these limitations, by the 1920s patients suffering from chronic intractable pain had as their only options psychotherapy or neurosurgery (ligation, resection or crushing of nerve fibers) to prevent the spread of pain to the spinal cord and brain (1,8-10).

Between the 1920s and **1970s limitations** on the use and prescription of opioids (opiophobia) imposed after the first epidemic, generated a time of under-treatment of pain in the health environment that would eventually generate reactions against these restrictions, as doctors considered that patients

Cancer patients were then encouraged to refrain from taking opioids until their lives could be "counted in weeks"

suffering from pain were being harmed as doctors were not able to offer the appropriate treatment to these patients. It begins a phase of concern about the infra-treatment of pain, which was driven by some publications and that ended up generating a movement in favor of the proper use of opioids in the treatment of pain (11-13).

Period iv 1973-1990: concern about under-treatment and poor management of pain, Porter, Portenoy, zenz and who. First approvals of modern opioids

1973, Marks et al: under-treatment or mal-treatment of pain (13)

Marks was one of many authors of the time who raised their voices to manifest the situation of under-treatment and poor treatment of pain. The author relied on 37 interviews with hospitalized patients treated with narcotic painkillers. 32 % of patients continued to have severe pain despite treatment and 41 % had moderate pain despite treatment. 63 % of patients received meperidine (50 mg every 3-4 h or less) and only 1 patient received doses greater than 75 mg. The average dose per patient per day was 90 mg. The authors concluded that there was a lack of information among doctors regarding dosages, duration of action of opioids as well as an exaggeration of the risk of addiction.

1983: Porter and Jick quantify the risk of addiction at 0.03% (14)

The authors relied on the review of 39,946 hospitalized and monitored patients of which 11,882 patients had received at least one opioid. Only 4 reasonably documented cases of addiction were detected in patients who had no history of addiction. The drugs involved in these cases were meperidine, percodan and hydromorphone. The authors concluded that the risk of addiction in hospitalized patients was minimal.

1986: Portenoy et al. demonstrate the safety of opioid treatment in patients with chronic intractable non-cancer pain (15)

The controversy over the use opioids in chronic non-oncological intractable pain was already in the medical circles of those years having on the one hand doctors who considered that this treatment was contraindicated in these patients (non-cancer) mainly because of the risk of addiction and on the other side, several medical groups that had reported a satisfactory use in patients with chronic non-cancer.

Portenoy's study (15) included 38 patients treated with opioids for at least 6 months for non-cancer pain of various etiology (back, mostly after disc surgery or trauma, facial, abdominal, pelvic, limb, post-herpetic neuralgia, benign tumor resection among others). Most patients were treated with oxycodone or methadone and half of them had been treated for 4 or more years. Only 2 patients presented some problem of management. Opioid treatment was started after the failure of several previous treatments. Of these 19 patients, 37 % had adequate pain relief, 32 % had partial relief and the others still had periods of severe pain.

The authors recommended the following guidelines for the proper use of opioids:

— Chronic opioid use is considered only when pain management attempts have previously failed and pain remains a major impediment at the functional level.
— This functional improvement with opioids must also be associated with cognitive behavioral and physical therapies.
— The commitment of a single doctor to evaluate medical treatment alongside psychological problems as well as pain is critical before starting chronic treatment.
— The doctor should evaluate the need to stop treatment in patients who do not get adequate control or any pain management.
— Sign informed consent.
— After dose adjustment, the patient should be seen once a month and given the medication for 1 month of treatment.
— The need for higher doses should be counted to ensure that use is adequate.

Portenoy recommended guidelines for the proper use of opioids

WHO 1986 (Cancer Pain Relief): analyzed the under-treatment in post-surgery patients and cancer patients (16)

In this document, WHO recognized pain treatment as a universal right and, for the first time, included opioids emphasizing that their effectiveness is beyond doubt and that properly used analgesics allow for pain control in up to 90 % of patients: "*It needs to be emphasized that relief is possible for the several million cancer patients who each day suffer unalleviated pain. Existing knowledge permits an approach to the problem that could be implemented on a worldwide basis. Analgesic drug therapy is an essential component of this approach; when used correctly, it is capable of controlling pain in more than 90 % of patients (16)*".

Increased mortality from illegal drug addiction in Europe between 1986-1990

In the **1980s and 1990s** there was an epidemic of illegal opioids in several countries in Europe, with an increase in addiction of 170 % and with a great variability between different countries (12). The ratio of addiction deaths was un-correlated with the increase in prescription opioids in these countries. The countries with the greatest increase in drug mortality were Germany, Italy, Spain, the Netherlands and the UK. Zenz et al. (12) found no direct correlation between the increase of prescription morphine use and the increase of drug mortality in these countries. In fact, the average dose of morphine prescribed per capita expressed in DDD 30 mg (defined daily doses) for the period 1986-90 was only 168 in Spain versus for example 1,438 from UK, 3,048 from Denmark, 196 from France or 212 from Germany among others. Spain was the 3rd country with the lowest average dose for this period and yet one of the countries with the highest increase in mortality from illegal drug addiction. At the same time, existing regulations in several European countries to control the prescription and dispensing of morphine managed to keep the level of use of morphine low. (e.g. in Spain the identification of the patient was required by the use of a "controlled substance prescription" and the validity was limited to 12 weeks). Zenz concludes that this epidemic was completely linked to drugs for illegal use and prescription opioids had no role in their origin or its development.

1987: FDA approves MST CONTINUS (oral morphine) (17)

It was the first opioid formulation to allow a dosage every 12 hours instead of every 4-6 hours.

1987: Institute of Medicine

Institute of Medicine recommends that health organizations conduct systematic pain assessments using quantitative measures (18).

1990: FDA approves Hardgesic (Transdermal Fentanyl) (17)

First patch formulation of an opioid that allowed up to 3 days of treatment with a single application.

Period V: 1990-2000 the idea of under-treatment expands, mainly in relation to cancer patients with severe pain. Aps, brussels conference, and pain as V vital sign

Opiophobia had spread globally and lasted until the middle of the 20th century causing an under-treatment of intense pain by "the undocumented and irrational fear that proper use will cause patients to become addicted" (Morgan JP 1985) (11).

1990: The president of the APS (American Pain Society) (19) states the lack of improvement in pain assessment and treatment over the past 20 years (18,20)

M. Campbell asks to approach the pain with a different approach:

— Pain specialists start asking for pain to "become visible".
— Give doctors and nurses bedside tools to guide them in the use of painkillers.
— Ensuring that patients are part of the pain communication process.

In 1986, WHO recognized pain treatment as a universal right

— Increase guidelines.
— Improving care systems.
— Collect patient satisfaction.
— Work with narcotics control authorities to promote the therapeutic use of opioids.

Laws and Regulations in Europe in 1991 (12)

In Germany, Austria and many of the countries of southern Europe, governments were very restrictive about opioid use (except in Belgium, the Netherlands and UK). In most countries it was and still is necessary to use special prescription forms and in countries such as Italy, Spain and Portugal doctors had to request these prescription forms personally to the authorities and even pay for them (Spain and Portugal). The patient also had to present identification before the doctor could prescribe opioids (Spain and Italy) (Table I). In Spain, an official prescription model of narcotics has been available since the Royal Decree of July 8, 1930. This legislation has been regularly updated in successive laws such as the order of April 25, 1994 regulating prescriptions and special requirements for the prescription and dispensing of narcotic drugs for human use as well as other subsequent laws to this day.

1993, conference in Brussels, Europe: statement on the use of opioids in cancer patients (12)

— The first goal should be to adapt the treatment of cancer patients and provide them with relief by any means.
— Cancer pain control programs do not conflict with drug abuse control.
— Governments and clinicians must work together to ensure both: cancer pain control and drug abuse control.
— A future European narcotics law must be based on scientific data on both effectiveness and abuse prevention.
— WHO guidelines on cancer pain relief provide an excellent foundation for improving standards in cancer pain management.
— No patient should live without pain relief when this relief is possible.
— At meetings of European pain specialists in Brussels 1992, they agreed on opioid treatment doses and durations according to the needs of each patient (12).

Tabla 1. Regulaciones de prescripción de morfina en varios países de Europa en 1992 (12)

COUNTRY	SPECIAL PRESCRIPTION FORMS	NEED TO PRESENT PATIENT IDENTIFICATION DOCUMENT	TEMPORARY LIMITATION OF PRESCRIPTION	PRESCRIPTION VALIDITY TIME
Denmark	Numbered special requirements	No		2 years
French	Prescription book	No	14 days	14 days
Germany	Numbered special requirements	No	7 days	7 days
Greece	Special forms	No	5 days	5 days
Italy	Ministerial prescription book: doctor must ask the school for medical	Certificate from the local health unit	8 days	10 days
Holland	Special information on the indication	No		10 days
Portugal	Official prescription book	No		10 days
Spain	Narcotics recipe talonary	Extra-therapeutic prescription card		
United Kingdom	No	No		13 weeks
Switzerland	No	No		12 weeks

In 1991 the number of opioid prescriptions dispensed at U.S. retail pharmacies was 76 million prescriptions (18).

1993: Zenz et al. express the urgent need to make opioids more available to cancer patients (12)

In Europe, Zenz and Willweber-Strumpf published in *The Lancet* (12) an article on the impact of pain on cancer patients:

50-80 % of patients were not having adequate pain relief event though for most of these patients simple and efficient relief with available treatments is possible. The authors referred to the WHO publication (16 and the estimate of Porter and Jick (patients with opioid treatment for cancer barely develop addiction, 0.03 %) (14).

Zenz and Wilweber-Strumpf identified the two main barriers to the treatment of cancer pain:

— Lack of training and specialization in pain treatment among prescribers.
— Opiophobia induced by control measures that had generated a fear of action between doctors and patients.

They also concluded that ***"the dose and duration of therapy should be dictated by the patient's pain and not by legal regulations" (12).***

1995: "V vital sign" (APS, American Pain Society) (19)

Campbell proposed in 1995 the idea of assessing pain as a vital sign, raising pain to the level of vital information to promote its evaluation and management.

1995: In December the FDA approved the controlled release form of OxyContin (Oxyicodone) (17)

The FDA approved the controlled release form of OxyContin (Oxyicodone) with a label saying that the risk of iatrogenic addiction is very rare and that delayed absorption reduced the risk of abuse. Very soon Oxycontin was a focus of attention around opioid abuse, which continued according to the FDA until the 2000s (17).

At the time of approval, the FDA considered that OxyContin's controlled release formulation would result in less potential for abuse as the active substance was absorbed more slowly and there would be no pharmacokinetic peak to promote abuse. The FDA relied on the history of similar products (MST Continus) used since 1987 without a significant number of reports of adverse effects of misuse or abuse. Despite this belief, the FDA warned about the risk of abuse in the product label (17).

In 1995, opioid prescriptions in the United States were 87 million annual prescriptions dispensed at street pharmacies (vs. 76 in 1991; 79 in 1992; 82 in 1993; 85 in 1994) (18).

Period VI: 1996-1999. Relaxation in regulation and control of opioid prescribing

1998: The Federation of State Medical Boards (21)

The Federation of State Medical Boards states that physicians would not receive excessive regulatory scrutiny if they prescribed significant amounts of opioids. *"Physicians should not fear disciplinary action from the Board or other state regulatory or enforcement agency for prescribing, dispensing, or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the usual course of professional practice"*.

1998, November: FDA approves Actiq (oral transmucosal fentanyl) (17)

The first approved treatment for cancer breakthrough pain. It was approved with restrictions on the distribution program to prevent:

— Accidental exposure of children due to the format type *"lollipop"*.
— Avoid potential abuse.

1999: Act 791 is passed in California (18)

In the HSC (Health and Safety Code) it was added that any health facility that adoptees this code should, as a condition of obtaining its license, include pain as an element to be evaluated at the same time as other vital signs. This evaluation should be collected in the patient's parameters as it was done with the other vital signs.

In 1999, opioid prescriptions in the United States were 116 million annual prescriptions in retail pharmacies (vs. 105 in 1998; 97 in 1997; 94 in 1996) (18).

In 1993, Zenz and Willweber-Strumpf published that 50-80 % of patients were not having adequate pain relief event though for most of these patients simple and efficient relief with available treatments is possible

Period VII: 2000-2009. First government, FDA and other agencies measures to control the prescription. Denunciation and conviction of Purdue Pharma. TJC standards of pain management

Year 2000, the United States Congress approves H.R. 3244; Title VI, Sec. 1603 (18)

The "decade of pain control and research" is established. Prescription-related overdose and death reports, especially for opioids, began to increase in the early 2000s, with OxyContin being at the center of the problem. The number of people who admitted to using OxyContin for non-medical purposes increased from 400,000 in 1999 to 1.9 million in 2002 and 2.8 million in 2003 (17). It is important to note that this implies a deviation from the legal prescription to an illicit use, that is, that prescriptions were being used for non-medical purposes and by persons who were not the intended recipients of the prescriptions. What these figures do demonstrate is the failure prescription and dispensing of opioids mechanism in the United States from the very first moments of the crisis as they were clearly insufficient to control the transfer of product from legal to illegal channel. At the same time, they demonstrate that the control mechanisms of Europe and in particular in Spain have been sufficient to ensure that medical prescriptions were used by and for intended medical use.

2000: The Drug Addiction Treatment Act (DATA 2000) (2)

It allowed doctors to prescribe Schedule III, IV, and V medications to treat opioid addiction and dependence.

2001: FDA amends slow release Oxycodone product label (17)

The FDA removes allusions to the low risk of addiction from the label.

2001: The Joint Commission TJC publishes standards in pain management (22)

As part of the effort to reduce under-diagnosis and under-treatment of pain, TJC introduced standards to improve the management of patients with pain.

- Rights and Ethics. Recognize the right of individuals to appropriate assessment and management of pain.
- Assessment of Persons With Pain. Assess the existence and, if so, the nature and intensity of pain in all patients, residents, or clients
- Education of Persons With Pain. Educate patients, residents, and clients and families about effective pain management.
- Continuum of Care. Address the individual's needs for symptom management in the discharge planning process.
- Improvement of Organization Performance. Incorporate pain management into the organization's performance measurement and improvement program.

TJC was based on the believe that unrelieved pain has adverse consequences on a physical and psychological level and patients have the right to proper pain management. In this sense, health organizations have to organize, support and coordinate activities and resources to ensure that the pain of all patients is properly identified and treated (e.g. to make an initial and regular assessment of pain, education to providers about diagnosis and treatment of pain, education to patients and families, taking into account cultural, spiritual values...).

The evaluation of pain in intensity and quality (type, frequency, location, duration) must be performed regularly. Pain was therefore considered another element of the patient's evaluation as it may interfere with their evolution (e.g.it interferes with the functional level or patient's participation in rehabilitation after surgery). These requirements were necessary and should be implemented in accredited hospitals, although they were generic standards that left great room for interpretation to hospitals in their actual implementation (concrete processes and policies to be implemented).

In 2001, 138 M of opioid prescriptions were made at street pharmacies in the United States reaching a peak of 219 M of prescriptions in 2011 (decreasing to 207 M in 2013) (Figure 1) (2).

The number of people who admitted to using OxyContin for non-medical purposes increased from 400,000 in 1999 to 1.9 million in 2002 and 2.8 million in 2003

2001: launch of U.S. inter-agency collaboration (17)

In order to develop a public education regarding opioid prescription abuse, a collaboration was launched between the FDA, SAMHSA, CSAT (center for substance abuse treatment) and NIDA (National Institute on Drug Abuse) (17).

In the same year, stricter warnings are added to OxyContin's label regarding misuse and abuse (17):

- Assist prescribers in choosing patients who would benefit from OxyContin
- The indication of use was changed from "moderate-severe pain when an analgesic is needed more than a few days" to "moderate to severe pain management when a continuous opioid analgesic is needed for an extended period of time"
- The label also added that OxyContin is not an appropriate product for on-demand pain or the immediate post-operative period if the pain is mild or is not expected to persist for extended periods of time.
- A boxed warning was added to reinforce the most relevant information regarding the risk of abuse and dependence, and the lab agreed to implement a Risk Management Program (RMP) to try to reduce the misuse and abuse of OxyContin.

2002: ISMP (Institute for Safe Medication Practices)

Report asking if efforts in Pain Relief have compromised safety (20) and the inter-agency working group had a meeting to discuss OxyContin and other slow-release opioids regarding abuse and diversion.

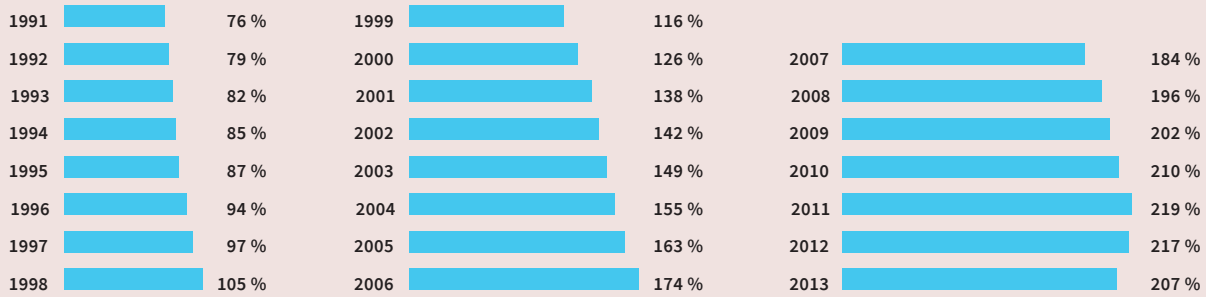
2002: FDA approves Buprenorphine and Buprenorphine/Naloxone (17)

Formulations that were accessible to primary care physicians trained specifically for its use.

2003: FDA sends warning letter to Purdue Pharma (17)

The FDA warns Purdue Pharma lab that it is using misleading advertising. Among other things, the FDA warns the company that its advertisements minimize or obviate the serious safety risks associated with OxyContin and promote use beyond the uses where the product has proven efficacy and safety. According to the FDA, the advertising and promotion of the product does not present the information contained in *boxed warning* regarding the potential risk of abuse (17).

Figure 1. Million opioid presciptions per year in USA for the period 1991 to 2013 (2)



2006: FDA generates a MG (Medication Guide) for Actiq (17)

MG is information to be delivered to all patients who are going to collect a prescription. Fentora, the second oral transmucosal product approved with MG and RMP (Risk Management Program) but without distribution restriction, is approved in September of that year (17).

2006: Reauthorization Act (2)

This Act increased the maximum number of patients that could be treated with buprenorphine per primary care physician going from 30 to 100 patients per doctor with the aim of promoting access to this treatment to patients with dependence.

2007: Purdue Pharma was convicted (17)

The lab was convicted of serious damage to federal charges related to Oxycontin's mis-promotion. As a result of this verdict,

Purdue Pharma arrived at a deal to pay a total of $634.5 millions as well as an additional $19.5 millions to 27 states. The accusations were based on the laboratory intentionally minimizing the risks of addiction and overestimated the benefits in treating chronic pain (23).

In September, the FDA held a public health advisory board around Fentora because medication errors had been reported that resulted in adverse events and death (17).

2007: September FDAAA (Food and Drug Administration Amendments Act) becomes law (17)

The FDA manages to expand its power as the authority responsible for designing and promoting drug safety, among other powers, the FDA may require REMS *(Risk Evaluation and Mitigation Strategies)* to ensure that the benefit of the drugs outweighs the risks. REMS requires laboratories to implement various safety measures on certain drugs and was the basis for the implementation of the future REMS program for all immediate and slow release opioids in 2009 and 2012.

2008: Cephalon apply new indications for Fentora (17)

Request the inclusion of non-cancer patients **with** breakthrough pain. The indication was not approved and in addition the FDA advisory committee considered that the existing RMP for the product was not effective so in February 2008 the FDA reviews Fentora's label and MG to increase warnings.

2009: FDA informs Cephalon that RMP is not enough (17)

FDA considers that the RMP of the product is not sufficient to ensure the safe use of Fentora for already approved indications and requests the laboratory to replace the RMP with REMS.

In April, the FDA and SAMHSA launched an initiative to ensure that the safe use of methadone, that appears to be the drug that has a disproportionate higher number of overdoses and deaths in patients compared to other opioids (17).

2009: in July Onsolis (transmucosal fentanyl)

Is approved for breakthrough pain in cancer. Approved with REMS. At this time the FDA decides that all similar products (transmucosal fentanyls) must share the same REMS (17).

2009: in August, Embeda (morphine/naltrexone)

Is approved as first product combining an opioid agonist and an opioid antagonist since 1982 (pentazocine/naloxone) for the treatment of pain (17). Also, at that time, according to the FDA, a significant number of opioid deaths and overdoses, especially with long-acting ones, are caused by theft or accidental exposure to the product so since 2009 the FDA has also been working with the DEA to educate the public about the safe disposal of drugs that are no longer needed (17).

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