

Overdose epidemic linked to the prescription of opioid analgesics in the United States

Epidemia de sobredosis relacionada con la prescripción de analgésicos opioides en Estados Unidos

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U ntil the 1980s, given their knowledge of the risk of addiction involved, physicians were more cautious regarding the prescription of opioids for treating pain in patients who were not terminal. However, an awareness-raising campaign aimed at US physicians and involving the dissemination of low quality evidence on the supposed efficacy and safety of opioid analgesics for the treatment of pain sparked the indiscriminate issuing of prescriptions and an even greater demand for opioid analgesics by patients.

A letter consisting of a single paragraph by Porter and Jick published in the *New England Journal of Medicine* in 1980 reported that 11,882 of 39,946 inpatients were prescribed an opioid, and that of only four who developed an addiction just one of them was severely addicted. The letter ended by saying that the development of addiction is rare in patients who do not have a history of addiction.

This letter has been cited 608 times over many years. In 72.2% of the citations it was taken as evidence that opioid addiction is rare, and 80.8% did not mention that the sample consisted of hospitalized patients. The message that the risk of addiction to opioid analgesics was small received widespread attention and may have contributed to the epidemic of opioid analgesics in North America. (Brauser, 2017; Leung, Macdonald, Stanbrook, Dhalla & Jauurlink, 2017).

The greater availability of opioids among the population triggered extensive growth in their use, with an atten-

dant rapid increase in the rates of abuse, addiction and overdose. When measures were tried to contain the epidemic, some people went on to take illegal opioids such as heroin or fentanyl and their derivatives. The increase in the number of deaths due to overdose has alerted the government of the United States to reduce their prescription and increase the range of treatments available to people who have developed addiction and have overdosed (CDC, 2016; Madras, 2017).

During the last two decades, sales of prescription opioids have increased by 300%, and more than 50% have been prescribed for the treatment of chronic noncancerous pain. Almost half of those being treated for addiction to opioids have reported that their first contact was via a prescription for pain treatment, and 80% of those with heroin addiction went through an earlier stage of opioid analgesics abuse (Madras, 2017).

It is estimated that 30% of Americans suffer some type of pain, half of them daily and considered serious in a third, with lower back pain and osteoarthritis the most frequent forms of chronic pain. Although opioid analgesics are prescribed for 20%, these produce a reduction of only 8-12 points out of 100 in lower back pain, and the treatment dropout rate due to lack of efficacy or adverse effects is as high as 50%. The authors point out that they are probably being prescribed too frequently or for too long for acute pain, and that their long-term efficacy for chronic pain is limited (Lin & Vega, 2016).

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Between 1999 and 2014 the number of deaths by overdose in the United States has quadrupled, with 61% of them linked to opioids. The rapid increase of such deaths - particularly in 2014 and 2015 - is linked in 72.2% of cases to synthetic opioids such as fentanyl, and to heroin in 20.6% (Rudd, Seth, David & Scholl, 2016; NIDA, 2017).

The Center for Disease Prevention and Control (CDC) of the United States states that 20% of those initially prescribed a 10-day course of opioid analgesics will continue taking these drugs for more than a year, which points to their addictive power. And it is also recognized that the simultaneous use of opioid analgesics and benzodiazepines (BZD) quadruples the risk of death by overdose, compared with the consumption of opioids without BZD (CDC, 2016).

1. Opioid addiction

The dilemma surrounding opioid analgesics is that they are essential medicines to relieve certain types of pain, but can at the same time cause great suffering to people who develop addiction and/or those who overdose.

Repeated supraphysiological stimulation of the dopaminergic system produced by the continuous use of opioids can induce changes in the plasticity of the brain (at the level of the glutamatergic system in the circuits linking the prefrontal cortex with the striatum), resulting in a decrease in the inhibitory control of seek and consume behavior, which can then become compulsive (Kalivas & Volkow, 2005) and which we know as addiction.

Opioids also have a double reinforcing effect, positive and negative. The positive is due to the brain mechanism of drug reward and euphoria. The negative is a consequence of its pain relief effect, not only physical but also emotional or psychic, caused by stressful or traumatic events. People suffering from a mental disorder therefore obtain a more powerful negative reinforcing effect and this makes them more vulnerable to opioid addiction (Guardia, Surkov & Cardús, 2010).

The risk of addiction also increases when their use diverges from the prescription made by the physician, either with higher doses or using a more direct administration route than the oral, or when they are consumed alongside other drugs or alcohol because dangerous synergies occur, with a high risk of overdose from such combinations (NIDA, 2012).

Epidemiology of opioid analgesic use

The United States has suffered an epidemic of opioid overdose deaths. In this country 91 people die every day as a result of overdosing on either prescribed opioid analgesics or illegal opioids. In 2016 there were more than 64,000 overdose deaths, including more than 15,000 involving heroin and more than 20,000 from synthetic opioids. The increase in overdose deaths that has occurred in the last decade has accelerated in recent years and it seems that

it may even result in a reduction in life expectancy of the United States population (NIDA, 2017).

This opioid abuse involves a cost of \$20 billion a year incurred by emergency services and hospital care. All this despite the lack of scientific evidence that these drugs are effective for the treatment of chronic pain, and the fact that they can also produce serious negative consequences, such as addiction, overdose, falls and injuries caused by accidents (Case & Deaton, 2015).

Heroin adulterated with fentanyl or its derivatives without the buyer's knowledge is increasingly sold on the black market. The risk of death from overdose is therefore much greater, given the power of fentanyl and its derivatives to suddenly paralyze the respiratory centers of the brain (EMCDDA, 2017).

Fentanyl is a synthetic opioid with 50 to 100 times the potency of morphine. Fentanyl derivatives, such as acetyl fentanyl, furanyl fentanyl, sufentanil, alfentanil, remifentanil, carfentanil, 3-methyl fentanyl, acrylfentanyl, butyryl fentanyl, parafluorofentanyl and others, can be a hundred times stronger than fentanyl itself. In particular, carfentanil is 10,000 times more potent than morphine and is used to immobilize and capture or anesthetize large animals (O'Donnell, Halpin, Mattson, Goldberger & Gladen, 2017).

Traces of several fentanyl derivatives can appear in the same person cases of in death by overdose. In the eastern states of the United States, half the deaths caused by opioid overdose tested positive for fentanyl and nearly half the overdoses from fentanyl or derivatives did not test positive for other illegal opioids, which suggests that fentanyl and derivatives may be emerging as illicit drugs in their own right. Since they are very powerful and have a very rapid effect, loss of consciousness and death are almost instantaneous and require immediate treatment with high or repeated doses of naloxone. In addition, in one in five deaths from fentanyl and derivatives there was no evidence of injection, with the drug being administered by other routes. Indeed, fake opioid analgesics tablets containing fentanyl or derivatives are in circulation (O'Donnell et al., 2017).

The number of overdose deaths involving prescription opioids has quadrupled since 1999, and since 2007 exceeds the number of deaths from heroin and cocaine overdoses combined. More than 77% of adolescents who have used heroin had previously taken opioid analgesics (vicodin, Percocet or OxyContin), which means that these drugs could be considered an entry drug to heroin for adolescents in the United States. The opioid analgesics that are most frequently abused are hydrocodone (Vicodin) - one in 12 - and oxycodone (OxyContin) - one in 20 (NIDA, 2017).

In Europe, overdose deaths have also been detected as a result of the administration of potent fentanyl derivatives among people with a history of heroin use (Hikin, Smith,

Ringland, Hudson & Morley, 2017), as well as an increase in non-fatal poisoning notifications involving powerful synthetic opioids such as fentanyl and derivatives (EMCDDA, 2017).

3. Overdose

Shortly after the administration of opioids, symptoms may occur of drowsiness, disorientation, sedation, sweating, miosis, and a severe slowing of breathing that may lead to respiratory arrest.

When we talk about overdoses, people think they must be heroin induced, and the media at times claim that they are due to bad quality or adulterated heroin. However, there are more overdoses in the United States today caused by opioid analgesics than heroin. The risk of overdose rises with greater heroin purity and when combined with fentanyl or derivatives, benzodiazepines or alcohol.

Although isolated benzodiazepine use does not usually produce clinically significant respiratory depression, it can exacerbate respiratory depression caused by opioids, and the risk of death from overdose increases substantially when benzodiazepines are prescribed to people already taking opioid analgesics (Horsfall & Sprague, 2016).

Jones & McAninch (2015) state that the prescription drugs most frequently behind overdose deaths are opioid analgesics and benzodiazepines (BZD) used simultaneously. According to the Center for Disease Prevention and Control (CDC) in the United States, the proportion of overdose deaths caused by opioid analgesics associated with benzodiazepines increased from 13% in 1999 to 31% in 2011. Between 2006 and 2011, deaths with BZD involvement increased 14% per year, while those involving opioid analgesics (without BZD) remained at the same level (Paulozzi, Jones, Marck & Rudd, 2011; Chen, Hedegaard & Warner, 2014). Moreover, half the patients suffering an overdose had received the prescription of both drugs from the same prescriber, even on the same day (Hwang, Kang, Kornegay, Staffa, Jones, & McAninch, 2016). That is to say that the co-prescription of opioids and benzodiazepines increases the risk of overdose and also of deaths due to overdose, with people suffering from respiratory diseases, cardiovascular diseases, and elderly or debilitated people at increased risk.

In a recent study involving 13,089 people suffering from chronic noncancerous pain, 42.3% had received a prescription of benzodiazepines (BZD) in the 30 days prior to death (Olfson, Wall, Wang, Crystal & Blanco, 2017). Another recent study has found that in 23.5% of cases, the prescription of opioids and BZD was simultaneous, despite the intensifying effect of BZD on opioid-induced respiratory depression (Horsfall et al., 2017). Moreover, the US Drug Abuse Warning Network (DAWN) has also confirmed that the simultaneous use of opioids with benzodiazepines or

alcohol increases the risk of overdose from 24% to 55%, compared to the isolated consumption of benzodiazepines (SAMHSA, 2014).

The risk of opioid overdose may be four times higher when benzodiazepines are involved than with isolated opioid use (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015) and they could be one of the causes of death in one out of every six opioid-related fatalities (Corkery, Schifano, Ghodse & Oyefeso, 2004). Finally, the risks of co-prescribing opioids with benzodiazepines are confirmed by the recent increase in the frequency of such co-prescription (Hwang et al., 2016) and by a disproportionate increase in deaths due to opioid overdose with benzodiazepine involvement (NIDA, 2017).

The US Centers for Disease Control and Prevention recommends providing naloxone to patients taking opioid analgesics combined with benzodiazepines, or if they have a history of alcohol or drug abuse, since they are at greater risk of overdose (CDC, 2016).

When a person suffers their first opioid overdose, they should start specialized treatment of their opioid disorder immediately because addiction is a disease that increases the risk of overdose and is therefore potentially life-threatening. Specialized treatment after a first overdose can prevent future accidental death. However, opioid analgesic users are unlikely to be diagnosed with opioid use disorder, and opioids often continue to be prescribed, even though a person has overdosed (Madras, 2017).

In Europe, overdose is the leading cause of death among high-risk drug users. Men make up 78% of such cases, with an increase in older users between 2007 and 2015 and a decrease in the group of younger users, reflecting the aging of the opioid-using population. In 2015, there were 8,441 deaths due to an overdose involving an illegal drug, which represents an increase of 6% compared to 2014. Spain also experienced an increase in overdose deaths between 2012 and 2015 (EMCDDA, 2017).

The Spanish public health system has some advantages that could help prevent a future epidemic of opioid analgesics and overdoses. The computer network linking hospital care services with primary health care and mental health and drug addiction centers allows access to unified clinical histories, which facilitates the coordination of the different physicians involved. The electronic prescription, to which all physicians in the public health service have access, avoids duplication and facilitates the supervision and control of prescription guidelines for medications. The computer registration of methadone prescription is also visible for any doctor in the network of drug addiction centers. The availability of treatment centers in the drug addiction network for people with substance addiction facilitates specialized treatment for their addiction. Finally, access to the public health system is free for the entire population, providing simultaneous treatment not only of addiction

but also of the medical and psychiatric comorbidities that addiction sufferer may have.

Nevertheless, we should beware of a certain trivialization and ignorance regarding the risks of co-prescription and polydrug use which increases the risk of accidents and overdoses. For example, in some hospitals, intravenous morphine is easily administered “on demand” to patients suffering severe pain. This regimen of opioid administration, which can be maintained for many days of hospitalization and sometimes until the patient leaves hospital, carries a greater risk of addiction, especially for people who already have a history of other addictive behaviors or a greater vulnerability towards them.

There is also a serious lack of knowledge regarding addiction as a common disease that can affect anybody and that requires specialized treatment. Such treatment frequently requires specific drugs, but some of these are not paid for by the public health system and others involve various difficulties in terms of prescription or acquisition, especially when obtaining them represents a burden for the patient or when the medication has a high price.

Other risk factors for fatal overdose lurking in our environments and which could emerge in the coming years are the prescription of high potency synthetic opioids - such as fentanyl and its derivatives - and the co-prescription of opioid analgesics and benzodiazepines. The consumption of benzodiazepines is very high in Spain, affecting 15.3% of women and 7.6% of men, increasing with age and rising to 27% of women and 11.3% of men in the 55 - 65 year age range (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2013).

4. Prevention

Treating pain long-term with opioid analgesics carries the risk of the patient developing tolerance and needing increased doses, of hyperalgesia and addiction. Follow-up and monitoring allows potential signs of abuse or misuse to be detected when the patient does not follow the prescribed prescription properly.

In 2015, the Department of Health and Social Services of the United States began a campaign to reduce the prescription of opioid analgesics and overdose deaths with three strategies: (1) educating and training doctors in pain treatment to reduce opioid prescription, (2) facilitating access to naloxone and (3) expanding the availability of treatment for opioid medication addiction, which also includes minors (Dowell, Haegerich, & Chou, 2016).

An electronic program to monitor opioid prescriptions and promote safe prescription practices has been developed. The CDC has developed a guide for prescribing opioids with the following recommendations: (1) limit the onset of abuse and addiction to opioid analgesics through better control by physicians, (2) expand drug treatments

(based on evidence) for people who have developed opioid addiction, (3) protect people addicted to opioids by providing easy access to naloxone in case of overdose, and (4) coordinate the actions of all professionals who serve them to optimize the detection of and treatment response for people who have suffered some overdose (CDC, 2016).

Other recommendations are the preferential choice of normal analgesics for the treatment of chronic pain, restricting the prescription of opioid analgesics to those cases in which the benefits in terms of pain and functionality are greater than the associated risks, setting treatment goals with patients including the possibility of withdrawing them if the benefits do not outweigh the risks, prescribe the minimum effective dose, carefully re-assessing benefits and risks if thinking of exceeding a daily 50 mg dose of morphine or equivalent, and avoiding prescription and simultaneous use of other opioids or benzodiazepines whenever possible. Doctors should also enter the prescription data into an electronic program that warns of possible doses or combinations of risk. And access to specialized treatment programs and medications such as buprenorphine or methadone should be offered and facilitated for people who have developed opioid addiction (Dowell, et al., 2016).

Opioid addiction is a mental disease that can be treated effectively, although several treatment episodes are sometimes required for the patient to recover completely. Treatment requires the administration of opioid receptor agonist drugs, such as methadone or buprenorphine (NIDA, 2012).

It is also worth weighing up whether the benefits of opioid analgesics are only small or moderate in the short term and uncertain in the long term, compared to their potential serious adverse effects. For example, the expected benefits of opioids probably do not outweigh the potential risks when treating headache or fibromyalgia, while ordinary analgesics combined with antidepressants and/or anticonvulsants may even be more effective and less risky. There is no evidence to show that opioid analgesics bring long-term pain benefit and, conversely, considerable proof of their possible negative consequences, such as addiction, overdose and injuries due to traffic accidents. Furthermore, there is some evidence to suggest certain benefits of non-pharmacological treatments, which are also more innocuous (Dowell et al., 2016).

In the treatment of severe acute pain, opioids may be necessary for bone fractures, nephritic colic, myocardial infarction and similar. However, for minor pain such as lower back pain, headache, fibromyalgia or toothache, normal analgesics, rest and physiotherapy may be even more effective than opioids (Lligoña, López, Henche, Guardia, Tuca, et al., 2017).

In the case of chronic pain opioid analgesics should not be considered as routine or first-line treatment, with the

exception of active cancer, palliative care or terminally ill patients. It is advisable to avoid their indiscriminate prescription whenever possible and as a first option it is preferable to use ordinary analgesics, which can be combined with adjuvant drugs such as anticonvulsants and antidepressants (Guardia Serecigni, 2017).

It has also been recommended that patients be warned of the adverse effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence and withdrawal symptoms when their administration is interrupted. Patients should also be alerted to their interference in the ability to drive safely, especially at the beginning of treatment, when the dose is increased or when other depressants, such as anxiolytics, hypnotics or alcoholic drinks are taken at the same time (CDC, 2016).

Given that the United States is suffering from an overdose epidemic caused by a period of indiscriminate prescription of opioid analgesics, and given that we still have time to prevent a similar epidemic in our country, we consider it appropriate to disseminate this information not only among medical professionals but also among the entire population because together we can all contribute to avoiding it.

Conflict of interests

The author has received financial assistance from the Lundbeck Laboratory to carry out a study on the reduction of alcohol consumption with nalmefene which is unconnected to this editorial.

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