

Health Policy Review


Zohydro™ Approval by Food and Drug Administration: Controversial or Frightening?

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The actions and regulations of the Food and Drug Administration (FDA) are crucial to the entire population of the US, specifically the public who take a multitude of drugs and providers who prescribe drugs and devices. Further, the FDA is relevant to investors, specifically in regards to biotech and pharmaceutical companies involved in developing new drugs. The FDA has been criticized for a lack of independence on the one hand and excessive regulatory and expanding authority without evidence and consistency of the actions on the other hand.

The FDA approved a single-entity, long-acting, hydrocodone product (Zohydro™, Zogenix, San Diego, CA) on October 25, 2013, against the recommendation of the FDA's own appointed scientific advisory panel, which voted 11 to 2 against the approval of Zohydro. Subsequent to the approval, multiple consumer safety organizations, health care agencies, addiction treatment providers, professional organizations, and other groups on the frontline of the opioid addiction epidemic have expressed concern. In addition, the US Congress and various state attorneys general raised serious concerns about the approval of Zohydro, which is highly addictive and may enhance the opioid addiction epidemic. Supporters of Zohydro contend that it is necessary and essential to manage chronic pain and improve functional status with no additional risk.

Over the past 15 years, prescriptions for opioids have skyrocketed with the United States consuming more than 84% of the global oxycodone and more than 99% of the hydrocodone supply. The sharp increase in opioid prescribing has led to parallel increases in opioid addiction and overdose deaths, surpassing motor vehicle injuries in the US. Recent studies assessing the trends of medical use and misuse of opioid analgesics from 2000 to 2011 have concluded that the present trend of the continued increase in the medical use of opioid analgesics appears to contribute to increasing misuse, resulting in multiple health consequences, despite numerous regulations enforced by multiple organizations.

The approval of Zohydro and its defense from the FDA were based on a misunderstanding of the prevalence of chronic severe disabling pain. Based on inaccurate data from the Institute of Medicine, in part caused by conflicts of interest, 100 million persons have been described to suffer from severe pain -- the correct number is 22.6 million.

This manuscript analyzes 3 important principles of drug approval and utilization based on safety, efficacy, and medical necessity. Based on the limited literature that the authors were able to review including that which was submitted to the FDA by the manufacturers, it appears the safety, efficacy, and medical necessity were not demonstrated. In fact, the study submitted to the FDA showed a 50% pain improvement in only 48% of the patients in the treatment group and 21% of the patients in the placebo group at 85 day follow-up. This is a statistically significant result but its clinical relevance is unknown. The FDA approval decision occurring against the backdrop of the advisory panel recommendation is concerning and may result in serious consequences in the future.

Key words: Chronic non-cancer pain, Food and Drug Administration, opioids, Zohydro, misuse, tolerance, addiction, dependency, medical necessity

Pain Physician 2014; 17:E437-E450

Since its establishment in 1906, the US Food and Drug Administration (FDA) has faced controversy with criticism from a myriad of governmental agencies and non-governmental organizations due to over- or under-regulation. The US Department of Health and Human Services (HHS) is divided into multiple components of which the FDA is a crucial agency. The FDA is currently separated into 5 centers to regulate food, drugs, cosmetics, animal food, dietary supplements, medical devices, biological goods, and blood products (1,2). The FDA monitors the testing of over 3,000 new drugs each year on nearly 200 million people to determine their effects, and issues multiple warnings about drug safety. Consequently, the FDA is relevant to investors, specifically in regards to biotech and pharmaceutical companies, since the FDA can literally make or break the stock of a small company involved in developing new drugs. More importantly, FDA actions are crucial to the entire US population, specifically the public who take a multitude of drugs and providers who prescribe drugs and devices. At a cost of \$1.8 million, a 2006 Institute of Medicine (IOM) report on pharmaceutical regulations in the US found major deficiencies in the FDA system for insuring the safety of drugs on the American market. The report called for an increase in the regulatory powers, funding, and independence of the FDA (3,4). However, critics of the FDA claim that the FDA already possesses excessive regulatory authority that is ever expanding and that their decisions and actions lack evidence and consistency (5-12).

Approval of Zohydro™ (Zogenix, San Diego, CA) (13) was, at best, controversial (14). The controversy is based on the FDA's decision to approve it despite the recommendation of the FDA-appointed scientific advisory panel, which voted 11 to 2 against the approval of Zohydro. All of the physicians and scientists voted against the approval of Zohydro; only the consumer advocates on the panel voted for approval. The FDA approved Zohydro, a long-acting, high-dose, single-entity hydrocodone formulation which is potentially highly addictive and may enhance the current opioid addiction epidemic. Multiple consumer safety organizations, health care agencies, addiction treatment providers, community-based drug and alcohol prevention programs, professional organizations, and other groups on the front-line of the opioid addiction epidemic have expressed concern and criticized the FDA's decision (14-20). In addition, the US Senate and House of Representatives, and various state attorneys general raised

serious concerns about the approval of Zohydro. These concerns led to hearings in Congress along with multiple lawsuits and corrective legislation being discussed (21-24). However, supporters of Zohydro contend that this drug is necessary and essential to manage chronic pain and improve functional status (15,16). Further, it has been argued that risks are no more than hydrocodone combinations or other long-acting opioids (24).

OPIOID EPIDEMIC

Over the past 15 years, prescriptions for opioids have skyrocketed. The US has about 4.5% of the world's population, but consumes more than 84% of the world's entire oxycodone supply and more than 99% of the hydrocodone supply (25-30). In addition, based on reports from the Centers for Disease Control and Prevention (CDC), the sharp increase in opioid prescribing has led to parallel increases in opioid addiction and overdose deaths (31-33). Since 1999, overdose deaths have skyrocketed, especially among middle-aged individuals prescribed opioids for chronic pain. Opioid analgesic overdose deaths have increased 415% in women and 265% in men (31). In fact, in 2008 more than 36,000 people died from drug overdoses and most of these deaths were caused by prescription drugs (32,33). One hundred people die from drug overdoses every day in the US, exceeding the deaths from motor vehicle injuries.

Recent studies assessing the trends of medical use and misuse of opioid analgesics from 2000 to 2011 (34,35) concluded that the present trend of the continued increase in the medical use of opioid analgesics appears to contribute to increasing misuse, resulting in multiple health consequences. Kenan et al (34), assessing the trends and prescriptions for oxycodone and other commonly used opioids in the United States from 2000 to 2010, showed that the number of opioid prescriptions per 100,000 persons increased by 35.2%, from 61.9% to 83.7% during the period from 2000 to 2009. The distribution of opioids to US pharmacies in milligrams per 100 persons increased by at least 100% for all selected opioids during the period from 2000 to 2010 (Figs. 1 and 2). The average size of an oxycodone prescription increased by 69.7% during the same period, while the average size of a hydrocodone prescriptions increased by 69.4%. The rate of deaths from opioid overdoses also increased steadily through 2008 and is likely to continue to increase in subsequent years. Atluri et al (35) assessed the trends in the medical use and abuse of opioid analgesics from 2004 to

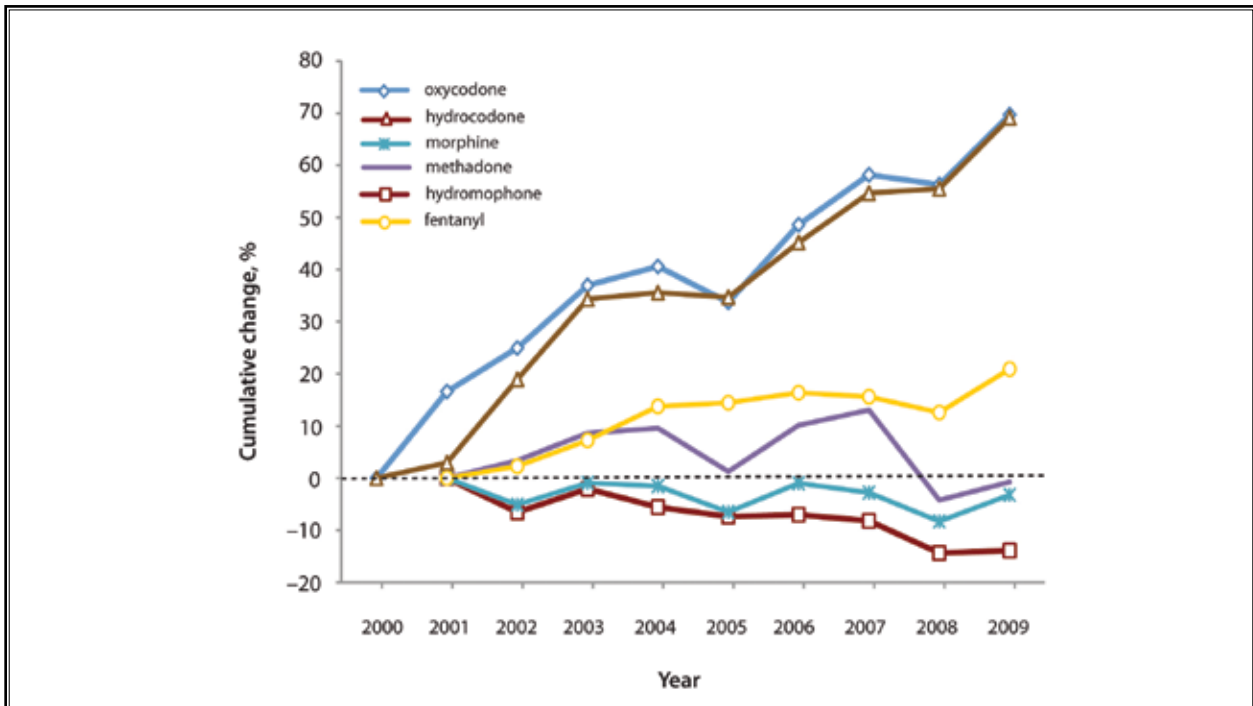


Fig. 1. Percent change in size of prescriptions (based on amounts in milligrams) for selected opioid analgesics in the US. Based on data from Vector One: National and Automation of Reports and Consolidated Orders System, for 2000–2009.

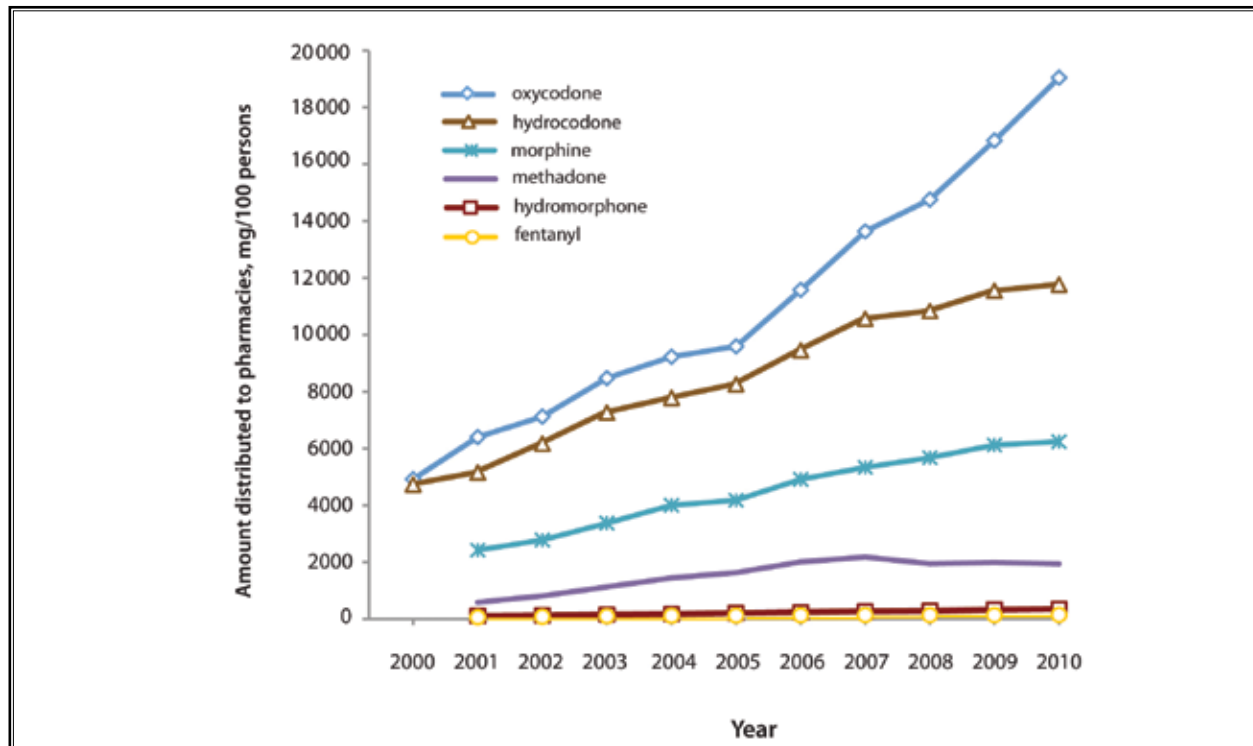


Fig. 2. Distribution of selected opioids to US pharmacies (in milligrams per 100 persons). Based on data from the Automation of Reports and Consolidated Orders System, 2000–2010.

2011. They showed an increase in the medical use of all opioids, except for a 20% decrease in codeine. The abuse of all opioids, including codeine, increased during this period.

Atluri et al (35) also showed that increases in medical use ranged from 2,318% for buprenorphine, 140% for hydromorphone, 117% for oxycodone, 73% for hydrocodone, 64% for morphine, 37% for methadone to 35% for transdermal fentanyl. The misuse increased 384% for buprenorphine with available data from 2006 to 2011, and from 2004 to 2011 misuse increased 438% for hydromorphone, 263% for oxycodone, 146% for morphine, 107% for hydrocodone, 104% for fentanyl, 82% for methadone, and 39% for codeine. They also showed that opioid use increased overall by 1,448% from 1996 to 2011, with increases of 690% from 1996 to 2004 and 100% from 2004 to 2011. However, misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 to 2004, and 245% from 2004 to 2011 (Fig. 3 and Table 1).

Paulozzi et al (36), describing the variation among states in prescribing opioids and benzodiazepines in the US in 2012, showed that prescribers wrote 82.5 opioid prescriptions and 37.6 benzodiazepine prescriptions per 100 persons. State rates varied 2.7-fold for opioids and 3.7-fold for benzodiazepines. For both opioids and benzodiazepines, the rates were higher in the South: 3 Southern states were 2 or more standard deviations above the mean. However, pain reliever prescriptions rates for long-acting or extended-release and high dose opioids were highest in the Northeast. The authors concluded that such high rates indicate the need to identify prescribing practices that might not appropriately balance pain relief and a patients' safety. Further, they also stated that such wide variations are unlikely to be attributable to underlying differences in the health status of the population. One possible explanation the authors mention is that there is a lack of consensus among health care providers on whether and how to use opioids for chronic non-cancer pain.

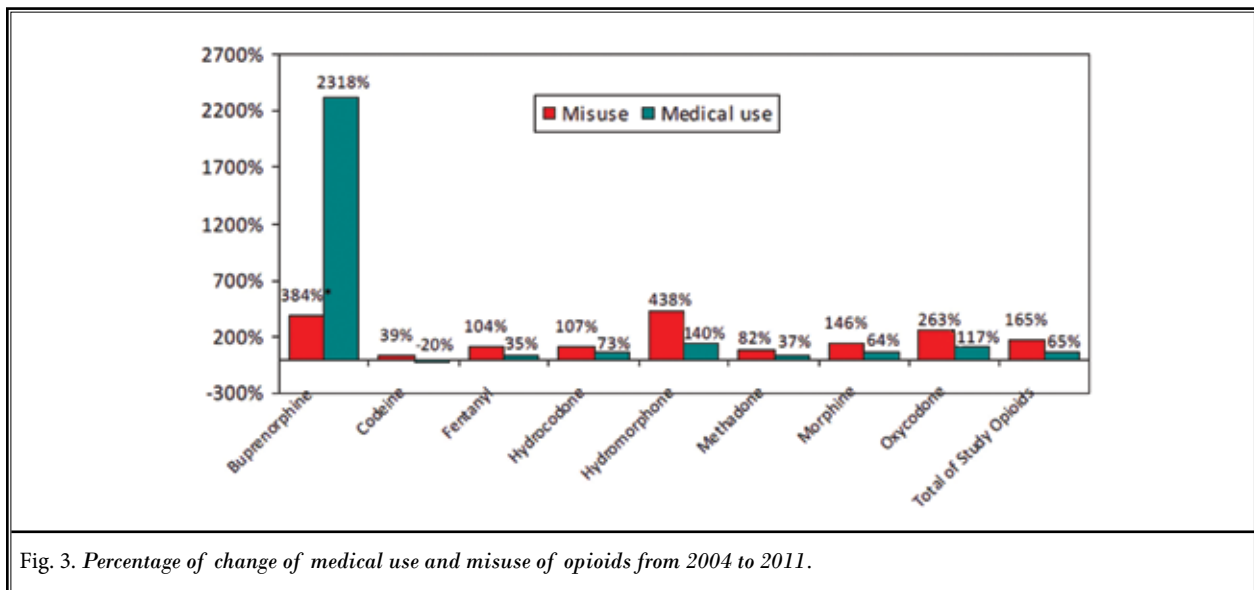


Fig. 3. Percentage of change of medical use and misuse of opioids from 2004 to 2011.

Table 1. Comparison of opioid use and misuse.

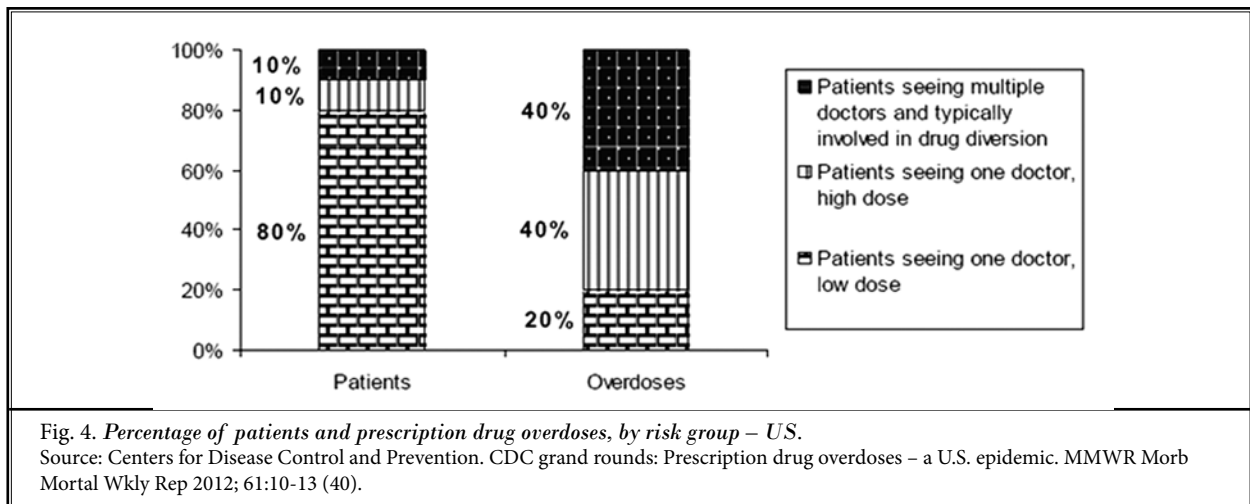
	Year			Percent change comparison		
	1996	2004	2011	1996 and 2011	1996 and 2004	2004 and 2011
Opioid Use	5,660,486	44,688,402	89,293,836	1,448%	690%	100%
Opioid Misuse (DAWN Visits)	4,688	68,999	224,069	4,680%	1,372%	245%

Adapted from: Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. Pain Physician 2014; 17:E119-E128 (35).

The growing epidemic in the medical use and abuse of opioids is closely linked to the economic burden of opioid-related abuse and fatalities in the US. It continues due to allegations of undertreatment of pain, with the introduction of long-acting opioids, a growing awareness of the right to pain relief, Joint Commission Accreditation of Healthcare Organization's (JCAHO) standards, and liberalization of laws governing opioid prescribing by state medical boards (26-46). Before 1990, physicians in the US took a minimalist approach to treating chronic non-cancer pain with opioids; however, opioids such as oxycodone and hydrocodone are now prescribed to one in 25 adults for the treatment of chronic non-cancer pain. The number of prescriptions written for opioids has increased 10-fold since 1990 (46). The current extent of opioid use in the US is unprecedented in the country's history and unparalleled anywhere in the world (34). The statistics are startling. In 1990, the world's population consumed 4 tons (3,628 kg) of hydrocodone, but in 2009 annual worldwide consumption had risen to 39 tons (35,308 kg), 99% of which was consumed by Americans (29). Similarly, 3 tons (2,722 kg) of oxycodone were consumed worldwide in 1990, and 77 tons (69,853 kg) by 2009, of which Americans consumed 62 tons or 81%. This has increased to 84% in 2012, despite numerous controls established by state and federal governments. Even though opioids may be beneficial for treating pain in carefully selected patients, their increased use in the US has included an increase in their nonmedical use. The long-term use of opioids has been associated with a spectrum of adverse effects, including fatal overdoses (31-33,39-41,44,47-71). It has been shown that opioid-related poisoning

causes a substantial burden in the US each year with a total estimated cost of approximately \$20.4 billion (42).

Recent epidemiologic research has revealed significant increases in the risk of adverse effects, even for what was considered as a low-dose of 50 mg or higher morphine-equivalent per day (26,43-45). Overall, the general impression among physicians is that low-dose opioid therapy is below 100 mg morphine-equivalent and high-dose is considered over 200 mg. Even then, 40% of deaths are related to high-dose opioid therapy, 40% are related to opioid abuse, and 20% are related to those receiving opioid therapy below 100 mg of morphine-equivalent (Fig. 4). It has been shown that 94% of patients who present to interventional pain management clinics are on opioids (53), and they continue to be on opioids even after they enter a treatment program. In fact, once a patient has been on opioids, they would like to continue on them forever, even if they are responding to other treatments (26,39,53). This fact has been emphasized in multiple manuscripts by Manchikanti et al (26,53) in the past. Recently Thielke et al (39) showed that over 80% of patients continued higher dose opioid use at one year, regardless of reported problems, concerns, side effects, pain reduction, or perceived helpfulness or helplessness. These findings suggest that it is difficult to reduce the opioid dose among chronic higher-dose opioid users. Further, patients who are receiving high-dose opioids for other than chronic pain, such as surgery, injury, and other issues, also tend to continue to request higher opioid dosages and/or become used to the effects of intermittent therapy with more potent opioids. Consequently, high opioid usage is not only dependent on



chronic pain and the particular opioids administered for chronic pain, but also experiences with acute pain and the opioids administered for management of acute conditions.

Overall, it now appears that even patients who have received opioids for 3 to 4 months require opioids for longer periods or the rest of their lives, making it difficult to reduce their dosages. This is reflected in the increasing opioid usage in the US despite multiple regulations and controls. In fact, these alarming trends led the FDA to deem prescription opioid overdose deaths an epidemic, thus prompting multiple federal, state, and local actions (72). The HHS' efforts aim to simultaneously reduce opioid abuse and safeguard legitimate and appropriate access to these medications is a tough position to be in. It has been stated that HHS agencies are implementing a coordinated, comprehensive effort addressing the key risks involved in prescription drug abuse, particularly opioid-related overdoses and deaths. These efforts have focused on 4 main objectives: providing prescribers with the knowledge to improve their prescribing decisions and the ability to identify a patient's problems related to opioid abuse; reducing inappropriate access to opioids; increasing access to effective overdose treatment; and providing substance-abuse treatment to persons addicted to opioids.

EXAGGERATION OF CHRONIC PAIN EPIDEMIC

While the Department of Justice and its agency, the Drug Enforcement Administration (DEA) are very aggressive in prosecuting drug abusers, the FDA and multiple HHS agencies do not seem to understand the relationship between opioids and their potential abuse. Thus, Zohydro, a single-entity formulation of hydrocodone, was approved on October 25, 2013. It thus joined a category of extended-release and long-acting oral opioids that includes OxyContin® (oxycodone HCL [Purdue Pharma, Stamford, CT]); 3 different versions of extended-release morphine sulfate: MS Contin® (Purdue Pharma, Stamford, CT), Avinza® (Pfizer, New York, NY), and Kadian® (Actavis Elizabeth, Elizabeth, NJ); Exalgo® (hydromorphone hydrochloride [Mallinckrodt, Dublin, Ireland]); Opana ER® (oxymorphone hydrochloride [Endo Pharmaceuticals, Dublin, Ireland]); Nucynta ER® (tapentadol [Janssen, Titusville, NJ]); and Embeda® (morphine sulfate and naltrexone hydrochloride [Pfizer, New York, NY]). The evidence is clear that long-acting opioids are more addictive and lead to higher dose therapy with a higher frequency of drug usage lasting a lifetime and are associated with major adverse effects

(25-28,35,39,43,46,48,63,70).

It was surprising that the FDA and other agencies continued to quote inaccurate chronic pain data from an IOM report (73) which was essentially based on a study by Gaskin and Richard (74). It reported the total incremental medical expenditures for selected pain conditions exceeded \$650 billion and the dramatic number of people suffering with chronic pain was 100 million (74). Unfortunately, the data was misinterpreted. This study from Johns Hopkins defined persons with pain as follows:

- Persons who reported that they experience pain that limited their ability to work, which is appropriate and includes 43.9 million of the total 100 million being estimated and discussed here, with 21.3 million suffering with moderate pain and 22.6 million suffering with severe pain.
- However, the number 2 category was persons who were diagnosed with joint pain, which was estimated to be 70.3 million and with arthritis of 53.4 million.
- Finally, they also included 24.7 million persons who had a disability that limited their ability to work that had nothing to do with pain.

Martin et al (75,76) also evaluated health care expenditures in the US in 2005 for treating back and neck problems. They found these expenditures to total approximately \$86 billion, with an increase of 65% between 1997 and 2005 and a 49% increase in the number of patients seeking spine-related care.

The discrepancy in the data presentation of the IOM, which was also adopted by other agencies including the Centers for Medicare and Medicaid Services, the US Government Accountability Office, and the FDA has been identified by the American Society of Interventional Pain Physicians (ASIPP) to be inaccurate, as shown in Tables 2 and 3 (72,77).

John Fauber of the Milwaukee Journal Sentinel on June 15, 2014, described the chronic pain statistic by IOM as exaggerated and misleading (78). The 100 million figure has become a central part of the debate over the use of narcotic pain killers and was used to justify Zohydro's approval. Margaret Hamburg, the FDA commissioner, turned to a sobering statistic when faced with intense criticism for her agency's approval of the powerful narcotic pain killer Zohydro: 100 million Americans are suffering from severe chronic pain (78). This has been cited in news stories, by medical organi-

zations, and by drug companies seeking approval for new opioid therapies (78). Fauber described that when Hamburg spoke in April at a prescription drug conference, she noted debilitating pain affects more people than heart disease, cancer, and diabetes combined. In fact, the number of people suffering with severe pain has been shown to be 22.6 million – not 100 million.

The Patient Protection and Affordable Care Act (ACA) required the federal government to enter into an agreement with the IOM, “to increase the recognition of pain as a significant public health problem in the United States.” Fauber reported that 9 of the 19 experts on the panel that produced the above numbers had financial connections to companies that manufacture opioids. In addition, some were officers or board members of groups that received opioid manufacturer funding and others were drug company consultants, or were paid through educational programs funded by companies that make pain drugs. ASIPP was not invited to participate in this panel and contradicted this number. In addition to ASIPP, others, including von Korff (78), also contradicted this number. While the IOM panel members denied any conflicts of interest, it is difficult to understand how one could misinterpret the numbers so drastically.

SAFETY CONCERNS OF OPIOIDS

Safety of opioids has been in the forefront of the war on drugs. Opioid adverse effects including death occur usually when they are abused; however, they can also occur when they are taken as prescribed. On September 10, 2013, the US Food and Drug Administration (FDA) announced class wide safety labeling changes

Table 2. *The prevalence and cost of chronic pain.*

- ◆ The annual cost of chronic pain is \$560 to \$635 billion a year
 - Direct cost due to pain is \$261 – \$300 billion
- ◆ Prevalence estimates
 - 10% moderate pain
 - 11% severe pain
 - 33% joint pain
 - 25% arthritis
 - 12% functional disability
- ◆ Moderate pain \$4,516
- ◆ Severe pain \$3,210
- ◆ Joint pain \$4,048
- ◆ Arthritis \$5,838
- ◆ Functional disability \$9,680

Source: Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724 (74).

and new post-market study requirements for all extended-release and long-acting (ER/LA) opioids analgesics intended to treat pain (79). The FDA evoked its authority to require safety labeling changes and post-market studies to combat the crisis of misuse, abuse, addiction, overdose, and death from potent opioids that have harmed too many patients and devastated too many families and communities as per the FDA commissioner Hamburg (78). The updated indication stated that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Further, the updated indication clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternate treatment options including non-opioid analgesics or immediate-release opioids

Table 3. *Total incremental costs of medical expenditures for selected pain conditions (in millions of adjusted 2010 US dollars and millions of persons).*

Condition	Population (in Millions)	Model 2 (including Functional Disability)	Model 3 (including Functional Disability, Diabetes, and Asthma)
Moderate pain	21.3	\$39,024	\$39,646
Severe pain	22.6	\$58,144	\$60,000
Joint pain	70.3	\$48,280	\$45,630
Arthritis	53.4	\$61,071	\$59,292
Functional disability	24.7	\$93,529	\$88,680
Total	100.0	\$300,048	\$292,257

NOTE: Dollar amounts were adjusted for inflation as of 2010 using the Consumer Price Index Medical Care Inflation Index. This analysis is based on the total noninstitutionalized adult subpopulation of the United States for individuals aged 18 or older, who represented 210,764,398 individuals as of 2008. Model 2 includes functional disability in addition to all the other control variables. Model 3 includes functional disability, asthma, and diabetes in addition to all the other control variables. One hundred million persons had at least one of the pain conditions studied. The population total for the selected pain conditions does not sum to 100 million because some persons have multiple conditions.

Source: Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724 (74).

are ineffective, not tolerated, or would be otherwise inaccurate to provide sufficient management of pain. The FDA's regulatory programs in the FDA Center for Drug Evaluation and Research (CDER) considers product labeling as the primary tool for informing prescribers about the approved uses of medications.

If the FDA approved abuse-deterrent labeling for reformulated OxyContin in April of 2013 and also issued a statement that the agency will not approve generics to original OxyContin. The FDA also indicated that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route "snorting" (80). Multiple drugs are available in the US market with abuse-deterrent reformulations which are crush and extraction-resistant including OxyContin® ER, Opana®

ER, Exalgo®, Suboxone®, Embeda®, and Aversion®. In fact, the number of individuals filling a prescription decreased after the reformulation of OxyContin 15% and for Opana ER 31%; and drug diversion decreased significantly for OxyContin, Opana ER, and other opioids and contacts involving intentional abuse of OxyContin, Opana ER and other opioids as shown in Figs. 5 to 7.

Thus far, evidence indicates increased safety and reduced usage of tamper-resistant formulations and abuse-deterrent reformulations.

Saga of the Approval of Zohydro

For any drug to be approved and utilized there should be safety, efficacy, and medical necessity. It appears that the FDA has failed to follow these 3 principles.

Safety

Zohydro is a high-potency opioid agonist sold in capsule form without features to deter crushing or injecting. The FDA explained that it approved Zohydro on the grounds that it is safe and effective for pain when used as directed and may reduce the risk of toxic effects on the liver because, unlike other hydrocodone preparations, it does not contain acetaminophen. However, this is in contrast to what occurred on December 22, 2013, when the FDA's own advisory committee voted 11 to 2 against the approval, calling for additional safeguards against inappropriate use and diversion. The attorneys general from 29 states have requested that the FDA reconsider its approval of Zohydro. In addition, Massachusetts' Governor Patrick declared a public health emergency over the loss of life from overdoses

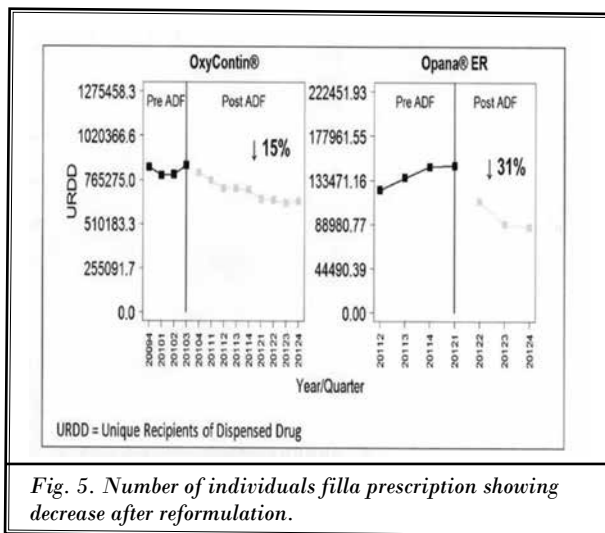


Fig. 5. Number of individuals filla prescription showing decrease after reformulation.

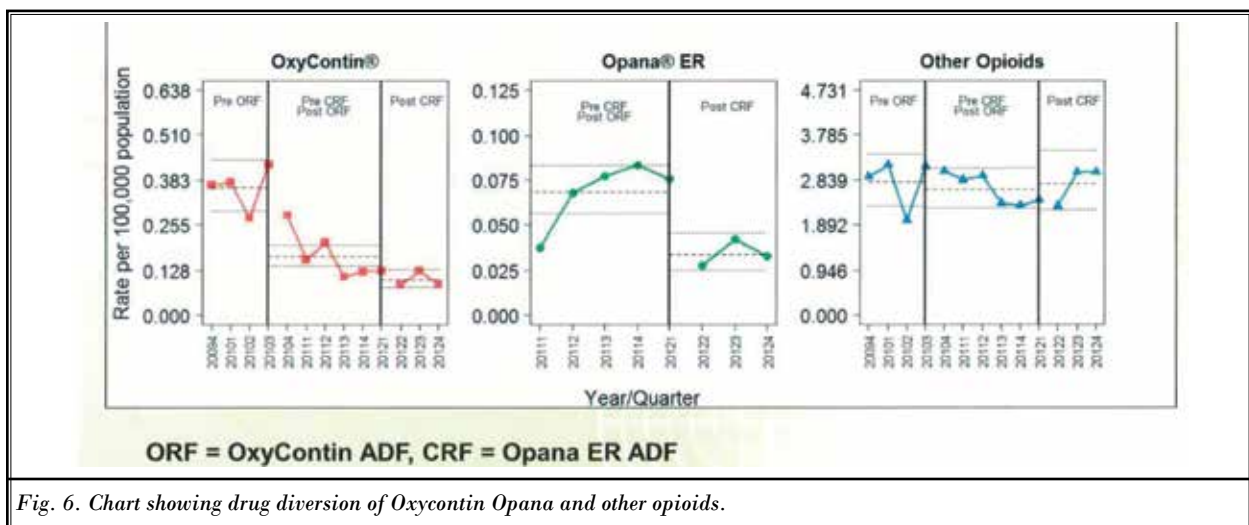
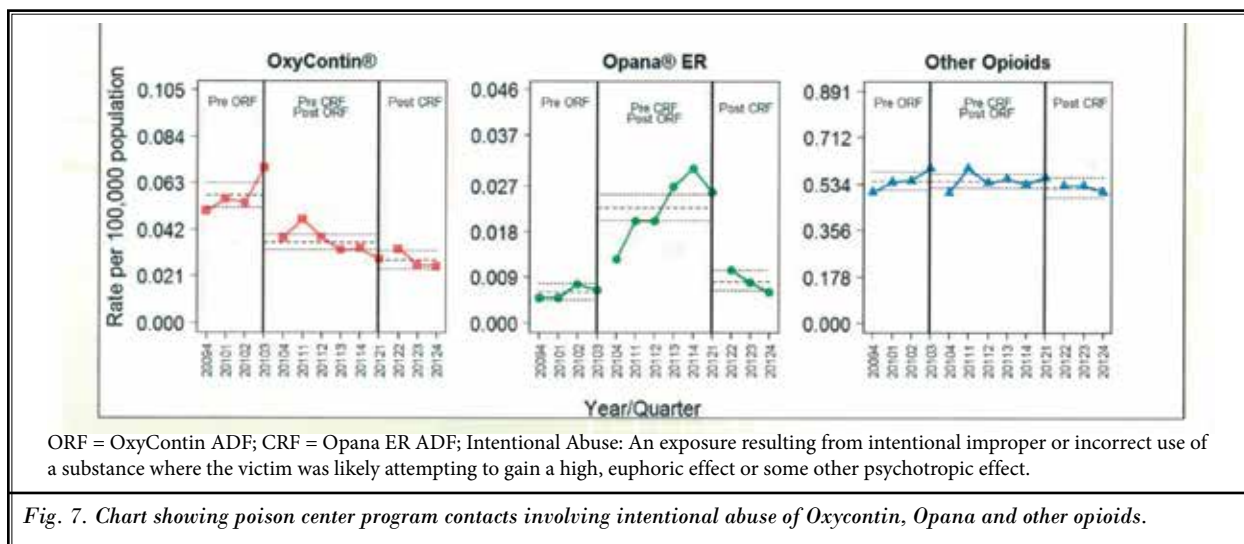


Fig. 6. Chart showing drug diversion of Oxycontin Opana and other opioids.



and the lack of abuse deterrent features of Zohydro and banned the prescribing and dispensing of Zohydro in Massachusetts; however, Zogenix, the manufacturer of Zohydro, quickly and successfully challenged the governor's action in federal court, which in turn struck down the decision by the Massachusetts governor. In this case, the court found that the FDA's federal authority pre-empted state law and that banning the medication would deny appropriate access for patients in pain. Multiple other states are taking different types of actions. The US Senate and the House of Representatives have introduced bills to reverse the FDA's decision and ban this drug based on safety.

It may be accurate that the federal government, specifically the FDA, CDC, and DEA, may be doing more than ever before about safety to respond to the overdose epidemic, but these actions have not reduced opioid use, misuse, abuse, and fatalities. These actions are not likely to reduce pressure from elected officials and distraught families grappling with an alarming loss of life from overdoses (17). Thus, a more comprehensive and coherent strategy, cutting across the breadth of US health care, is urgently needed, and should include approval of drugs based on scientific evidence, safety, efficacy, and medical necessity.

The makers of Zohydro have argued that long-acting hydrocodone preparation without acetaminophen will reduce a multitude of adverse effects, not only related to hydrocodone, but acetaminophen. As shown in the data of abuse-deterrent reformulations (Figs. 5 to 7), there was not only decrease of filling prescriptions after reformulation, but there was also decrease of drug diversion as well as poison center program con-

tacts involving intentional abuse. Zohydro lacks this safety, consequently, an average hydrocodone preparation with 5 to 10 mg of hydrocodone, is only 1/20 or 1/10 as potent. Consequently two Zohydros crushed and injected can be fatal for adults and one Zohydro could be fatal for children. The benefits of not including acetaminophen may also have been exaggerated as the deaths related to acetaminophen are less than 200 liver failures linked to acetaminophen with over 80% of them being suicide attempts, translating to approximately 20 to 40 liver failures a year due to acetaminophen in contrast to over 16,000 overdose deaths due to opioids (81).

Zohydro's approval was based on safety findings from studies of 1,512 patients exposed to at least one dose of Zohydro ER, 332 patients exposed for at least 6 months and 290 patients exposed for at least one year. Thus, the majority of the patients were exposed for less than 6 months (82). For the study, the maximum dose was 200 mg per day; however, in the open label study, the maximum dose was up to 600 mg per day. The safety criteria were deficient on long-term follow-up as well as high dose administration. In fact, there were 5 deaths among the 575 patients in the chronic pain population exposed to Zohydro ER. The authors presenting the data to the FDA attributed only one death to Zohydro over dosage; however, a total lack of relationship to hydrocodone has not been defined in other deaths. They also reported that 81 patients exposed to Zohydro reported a total of 118 nonfatal serious adverse events. The majority of the side effects occurred in patients receiving Zohydro rather than placebo.

Overall, at least one medically serious adverse

event was reported in 9.7% of the patients, whereas in 10.5% of the population, or 121 patients, adverse events led to discontinuation of more than one patient in the chronic pain population. The most common adverse events leading to study discontinuation were nausea, somnolence, headache, constipation, vomiting, lethargy, fatigue, and cognitive changes. Serious adverse events included anxiety, mental impairment, small bowel obstruction, and abdominal distention or constipation. In the long-term open label safety study, the common adverse events were constipation (11.3%), nausea (10.7%), somnolence (7.7%), headache (7.5%), vomiting (4.1%), insomnia (3.8%), fatigue (3.6%), diarrhea (3.1%), dizziness (2.8%), dry mouth (1.9%), and pruritus (1.7%). In the treatment phase, the most common adverse events were constipation (12.5%), back pain (11.1%), nausea (9.9%), vomiting (9.7%), arthralgia (7.8%), headache (6.8%), urinary tract infection (6.6%), upper respiratory tract infection (5.9%), falls (5.9%), anxiety (5.4%), nasal pharyngitis, sinusitis, and insomnia (around 5%). Somnolence, fatigue, confusion, and dizziness were reported by 3%-4% of the patients.

The Zohydro application also described 92 diversion-related adverse events in one study and 63 diversion-related events in another study. The FDA concluded that the safety data provided by the applicant demonstrated that during the development of Zohydro ER, the safety profile was consistent with other extended release opioid analgesics when used as labeled in patients with chronic pain who require treatment with an around-the-clock opioid analgesic.

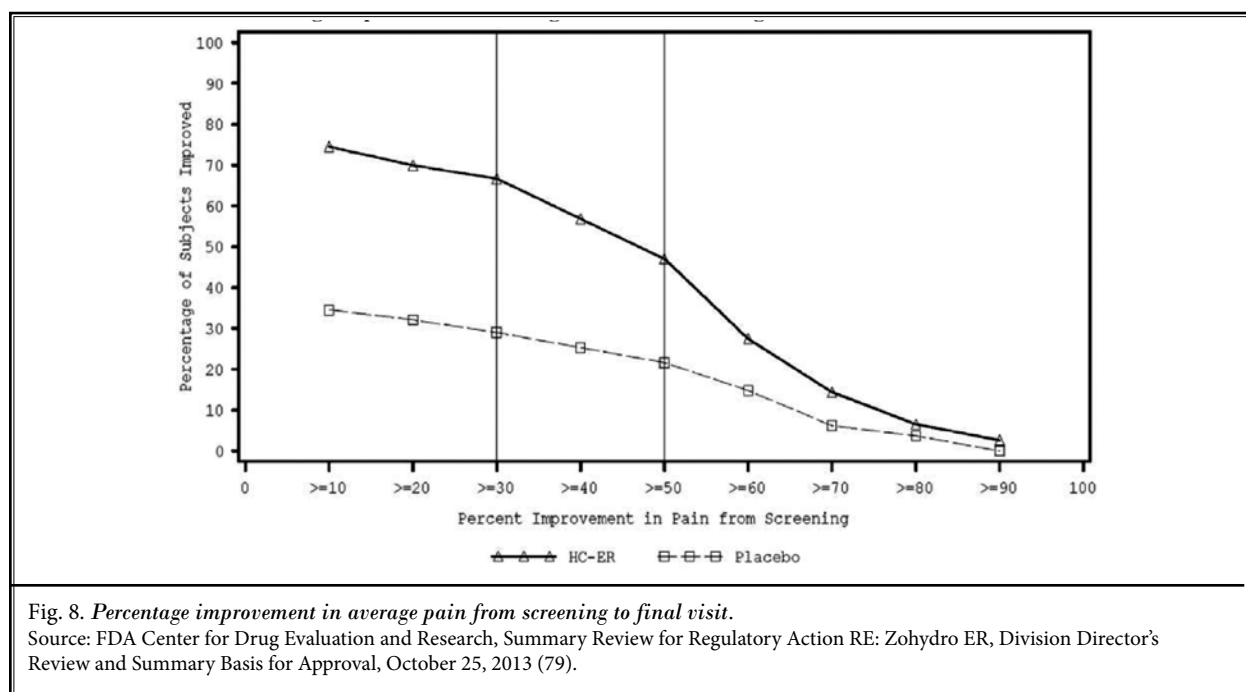
When OxyContin was launched in 1996, reports soon surfaced that the medication was being misappropriated and abused. Like Zohydro, OxyContin was designed to release medication slowly over a period of time, but addicted individuals soon realized that by crushing up and snorting the tablets they could receive the entire dosage all at once. Subsequently, OxyContin was reformulated so that it was more difficult to manipulate for purposes of misuse. However, the new drug Zohydro does not have any abuse deterrent technology, and since it is available in such high dosages, thrifty drug users could potentially get quite a bit of hydrocodone all at once. Zohydro, like other opioids, causes euphoria, which ultimately increases dependency and addiction.

The maker of Zohydro has presented information that they will be working on designing an abuse deterrent formulation (ADF). All concerned, including the FDA, recognize that Zohydro likely will be abused and/or diverted by individuals whose motives are other than

the intended use of the product. They argue that it is no different than any other opioid analgesic, immediate-release or extended-release, on the market; however, one may ask "why introduce another product into an already busy market"? Zohydro as a non-ADF opioid analgesic will be misused by individuals easily by crushing it and by those who swallow intact dosage units when they are not prescribed. Proponents of Zohydro argue that this is unfortunate and entirely foreseeable; it is only somewhat preventable, even with one ADF controlled-release opioid analgesic currently on the market. Multiple systematic reviews and guidelines have shown a lack of efficacy of chronic opioid therapy for managing chronic non-cancer pain as relates to a decrease in pain and improvement in function. Chronic opioid therapy is also associated with adverse effects. Thus far, there is no strong evidence for any opioid beyond 12 weeks (25-28,30). Even though Zohydro is not approved for as-needed pain relief, it will be used as such with 2 doses per day and supplementation with immediate-release hydrocodone, oxycodone, or other drugs used for so-called breakthrough pain (80).

Effectiveness

The efficacy and effectiveness determinations were made based on the study submitted to FDA in its approval of Zohydro ER (79); however, there were no independent trials or studies to determine the long-term efficacy or effectiveness. The inclusion criteria were patients with chronic low back pain of at least 3 months; nonneuropathic, neuropathic, or symptomatic for more than 6 months after low back pain surgery; those requiring around-the-clock opioid therapy; those taking opioids for at least 5 days per week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg of oral morphine equivalent; and an average pain score of greater than 4 on the 11 point (0 to 10) Numeric Rating Scale (NRS) for the last 24 hours of the screening phase. Exclusion criteria were respiratory depression; chronic constipation; a history of illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse; positive drug screen for illicit drugs, or unprescribed controlled substances; severe depression or anxiety; active fibromyalgia or other pain syndromes; spinal back pain pathology; conditions that would interfere with the assessment of low back pain; obesity; an allergy to any of the study drugs. As in other randomized and efficacy trials, this study had strict inclusion criteria which are not feasible in practical settings. Thus, lesser efficacy and more side effects



are expected in practical settings.

The primary efficacy endpoint of the study was the change from baseline randomization to the end of the double-blind maintenance treatment phase (day 85 or last visit) in average pain intensity on the 11 point NRS as recorded daily in an electronic diary, comparing Zohydro ER with placebo. The secondary efficacy endpoints included the response rate, with response defined as a 30% improvement from the screening pain intensity score to the day 85 pain intensity score, and the subject global assessment of medication.

A change in NRS scores does not appear to be a minimally required improvement. In addition, the study defines 30% improvement as significant. Generally, significant improvement has been defined as 50% or more (82).

The results showed that 183 patients completed the treatment phase, with 124 of 151 who received Zohydro completing the trial, whereas only 59 of 151 who received a placebo completed the trial. The most common reasons for discontinuation after randomization in the Zohydro ER group were a lack of efficacy (9%), noncompliance with the study drug (3%), and an adverse event (1%). The most common reason for withdrawal from the placebo group was a lack of efficacy (42%), followed by noncompliance with the study drug (5%), and an adverse event related to opioid withdrawal (5%). Further, the authors postulated that the large proportion of dropouts from the placebo group was

likely due to the small amount of rescue medication allowed during the trial after randomization (a maximum of 10 mg of hydrocodone per day).

The dropout rate of 18% falls within the generally accepted criteria of dropout of 20%; however the dropout rate of 61% in the placebo group is inordinately high. We believe this is indicative of the difficulty of conducting placebo trials, not only with interventional techniques, but also with drug therapy (82). Consequently, the intent-to-treat analysis takes precedence here, providing extrapolated data rather than collected data. The authors concluded that Zohydro ER was superior to placebo in change from baseline to the end of the study and averaged their daily pain intensity score with a *P* value of 0.008 and a mean change of 0.48 in the treatment group and 0.96 in the placebo group with a range of -3.0 to -5.3 in the treatment group and -2.4 to -6.7 in the placebo group.

The authors also have depicted in a graphic format the percentage of patients who achieved improvement across all possible cutoffs, which appears to be 30% of them with a 30% improvement as shown in Fig. 8. Further analysis of this graphic display shows ~68% in the treatment group and ~29% in the control group improving at $\geq 30\%$ improvement in pain from screening with a decline to ~48%; ~21% at $\geq 50\%$ percent improvement in pain from screening, and a decline to less than 10% in both groups with no significant difference

between the groups at $\geq 90\%$ percent improvement in pain from screening.

In addition, the analysis of rescue medication use during the double-blind treatment phase was also similar in both groups. The mean total daily dose of rescue medication in the treatment group was 6 mg \pm 3.4 mg, with a range from 0.1 mg to 12.5 mg, whereas in the placebo group, the mean dosage was 7.5 mg \pm 3.9 mg. However, it is rather surprising and confusing to see that while only 2 tablets of rescue medication totalling 10 mg were provided, the ranges were as high as 12.5 mg in one group and 20 mg in the other group.

Based on a review of the data, it appears that 30% more patients improved at 30 days, 25% at 50 days, and less than 5% at 90 days. In a practical setting, these data are not considered as showing the efficacy for Zohydro in a chronic pain population with a 3-month follow-up. There was also an extremely high dropout rate, significantly higher improvement in the placebo group's average mean pain intensity scores. The results showed that of the total 510 patients enrolled, only 302 (59%) completed the conversion/titration phase and were randomized to treatment and 208 (41%) discontinued the conversion/titration phase early. The most common reasons for discontinuation early from the conversion/titration phase included protocol violation, noncompliance with the study drug, adverse events, and a lack of efficacy.

In this study, patients were provided rather high doses of an opioid with a minimum of 40 mg to a maximum of 200 mg per day. During the taper, the patients also received Zohydro ER. Further, they were all allowed rescue medication, which is a red flag for the future to encourage a patient to use breakthrough medication which only increases the use of opioids by combining

long-acting and short-acting opioids (11,12,80).

Medical Necessity

While data on safety and efficacy are not robust and lacking to a great extent for Zohydro, there are numerous opioids already available on the market, along with similar products in safe formulations. Without assessing the known serious risks of misuse, abuse, opioid hyperalgesia, addiction, overdose, and death associated with long-term use beyond 12 weeks, the medical necessity of this drug is not proven. The FDA advisory committee has spoken on this issue clearly with a preponderance of negativity. The majority of the pain management community, as well as the scientific community, addiction management professionals, community organizations, Congress, multiple state agencies, and governors have spoken against the approval of Zohydro for good reasons..

CONCLUSION

With the ever-increasing explosion of therapeutic opioid use, overuse, abuse, misuse, tolerance, addiction, dependency, and adverse effects including death, the medical necessity of opioids in chronic non-cancer pain should require overwhelming evidence and safety demonstration prior to approval of powerful, new drugs. The case study of Zohydro approval demonstrates that the FDA can make decisions that fly in the face of a significant majority of the advisory committee which was itself put together by that same agency. We are concerned that this approval process was based fundamentally and a mistaken presumption of the chronic pain circumstance in the United States and that Zohydro use may lead to serious consequences in the future.

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