IT'S NOT JUST HEROIN ANYMORE:

EVOLVING ROLE OF FENTANYL IN DRUG OVERDOSE

By Phil Walls, RPh and Michael Nguyen, PharmD

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myMatrixx published a research paper, in 2015, entitled *A Brief History of Heroin Use in the United States: Evolving impact on Rx Drug Abuse*. Among other things, that paper highlighted the similarity between heroin, which is an illegal Schedule I controlled substance, and prescription opioids, many of which are used in the treatment of injured patients. In addition, it pointed out that addiction to prescription opioids results in an individual being 40 times more likely to be addicted to heroin.[1] Furthermore, deaths from heroin overdose increased by a factor of five from 2010 to 2016. However, it has been reported in multiple outlets that many of these deaths are not caused by heroin alone, but instead involve illegally manufactured fentanyl, which can easily be mixed with white powder heroin.[2,3]

Currently, this latest danger in the opioid overdose epidemic has primarily been identified in states east of the Mississippi River. This geographic affect is because white powder heroin is not as prevalent west of the Mississippi where black tar heroin is the predominant form. The black tar heroin is not as easy to mix with fentanyl powder,[4] and as a result, fentanyl is not as likely to be involved in an overdose west of the Mississippi.

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Patients who had become addicted to their prescription opioid turned to heroin, and deaths from heroin overdoses began to rise in 2010.

BACKGROUND ON FENTANYL

A Belgian physician and scientist named Paul Janssen first synthesized fentanyl hydrochloride in 1960.[5] Dr. Janssen also founded the present day drug company Janssen Pharmaceuticals, Inc.

Fentanyl citrate (the salt form combination of fentanyl HCl and citric acid) entered medical use in 1968 as an aqueous solution for intravenous or intramuscular injection. It was FDA-approved for use as a surgical anesthetic marketed under the trade name Sublimaze.[6] For this purpose, fentanyl citrate fit the utility criteria better than morphine because it had a faster onset of action, shorter duration of action, and was better tolerated (e.g., fewer side effects such as nausea, vomiting and histamine reactions).

To broaden its utility beyond surgical anesthesia, Janssen Pharmaceuticals introduced the Duragesic patch in the 1990s. The Duragesic patch was a technological enhancement that circumvented the short duration of action of fentanyl by allowing the drug to be slowly absorbed through the skin (transdermal) over a 48 to 72-hour period. For this reason, Duragesic was approved by the FDA for the "management of persistent, moderate to severe chronic pain in opioid-tolerant patients when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[7] However, because of the high potency of fentanyl (100 times greater than morphine), the FDA does not allow Duragesic to be used in opioid-naïve patients. Patients must be opioid tolerant before starting Duragesic, which is defined as those who have been taking morphine 60 mg/day or more, oral oxycodone 30 mg/day or more, oral hydromorphone 8 mg/day or more, oral hydrocodone 60 mg/day or an equianalgesic dose of another opioid for a week or longer.[8]

For the purpose of treating chronic persistent pain, Duragesic has a legitimate medical purpose when used appropriately: it provides a chronic pain patient with a constant and consistent delivery of medication that circumvents the need for manual dosing. Duragesic is included on the World Health Organization (WHO) Model List of Essential Medicines. Drugs identified on this list are those that the WHO considers to be "the most efficacious, safe and cost-effective medicines for priority conditions."[9]

continued BACKGROUND ON **FENTANYL**

Following the development of the Duragesic patch, which can be used for chronic pain of various etiologies, the pharmaceutical industry found a therapeutic purpose for fentanyl's rapid acting and short duration of action: breakthrough cancer pain. Breakthrough pain is defined as, "transient, severe pain occurring against a background of stable, persistent, adequately controlled pain."[10] Patients who were already on a stable regimen of a long-acting opioid can experience surges of severe pain. Thus began the endeavor to develop fentanyl into formulations that are fast-acting and short duration. Actiq was the first product in this class. Actiq is a solid form of fentanyl citrate produced as a berry-flavored lozenge attached to a handle. Commonly referred to as the Actiq lollipop, this fentanyl product was designed to be partially absorbed through the oral mucosa, which allows for the fast onset of action (5-15 minutes) and greater bioavailability (the amount of medication that is absorbed into the bloodstream). If swallowed whole, the onset of action is slower and the bioavailability is reduced. This is because when swallowed, fentanyl is absorbed into the bloodstream through the small intestines and relies on the slowness of the digestion process; the drug also undergoes partial drug degradation by the liver, a process known as first-pass metabolism.

Perhaps owing to the success of Actiq, many other drug companies developed their own formulation of fentanyl for the treatment of breakthrough cancer pain. The common attribute of these similar products is that they utilize routes of administration that provide faster absorption than oral administration. Most of the available products are formulated for absorption through the oral mucosa (e.g., sublingual solutions and tablets, buccal lozenge/tablets) and one product is formulated for nasal administration.

Despite the fact that all available immediate-release fentanyl products are only FDA-approved for breakthrough cancer pain, practitioners are known to prescribe them off-label for breakthrough pain of various etiologies such as chronic back pain. This is highly controversial because, although a lot of discussion has focused on the intense potency of fentanyl, the extremely short duration of action is a grave deficiency of the drug because it necessitates compulsive, habitual re-dosing.

100x

FENTANYL IS 100x MORE POTENT THAN MORPHINE

IMMEDIATE-RELEASE FENTANYL PRODUCTS FOR **TREATMENT OF BREAKTHROUGH CANCER PAIN**

TRADE NAME	CHEMICAL FORM	DOSAGE FORM/ ROUTE OF ADMINISTRATION	FDA-APPROVED INDICATION
ACTIQ	**Citrate**	**Buccal Lozenge on a Handle**	ACTIQ is indicated for the management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
SUBSYS	**HCl**	**Sublingual Liquid**	SUBSYS is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
LAZANDA	**Citrate**	**Nasal Solution**	LAZANDA nasal spray is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
FENTORA	**Citrate**	**Buccal Tablet**	FENTORA is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
ABSTRAL	**Citrate**	**Sublingual Tablet**	ABSTRAL sublingual tablets are indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
ONSOLIS	**Citrate**	**Buccal Soluble Film**	ONSOLIS is an opioid analgesic indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Table 1: Immediate-Release Fentanyl Products for Treatment of Breakthrough Cancer Pain.
Onsolis was discontinued for the reformulation that was approved in 2015. Anticipated relaunch is unknown at this time.

THE U.S. OPIOID EPIDEMIC AND
THE ROLE OF ILLICIT FENTANYL

The U.S. opioid epidemic is often discussed metaphorically as a swing of the pendulum. In the 1970s, opioids were considered highly addictive and doctors generally avoided prescribing them. The first push of this pendulum is often traced to a 1980 New England Journal of Medicine letter co-authored by Dr. Hershel Jick in which he declared, "...the development of addiction is rare in medical patients with no history of addiction."[11] The medical community gradually started to ramp up their treatment of pain with some referring to it as the fifth vital sign. The introduction of OxyContin (an extended release formulation of oxycodone) by Purdue Pharma in 1996 can be considered a shove of the pendulum. Purdue Pharma began a very effective marketing campaign to persuade doctors to prescribe OxyContin as a safe and non-addictive painkiller. By 2010, OxyContin accounted for 30% of the prescription opioid market with $3.1 billion in sales.[12] Opioid overdose deaths tripled from 1999 to 2008, prompting the Centers for Disease Control and Prevention (CDC) to declare that the U.S. was in the midst of a national opioid epidemic.[13] National attention followed and through widespread efforts, prescriptions for opioid painkillers began to decline. In 2017, the number of opioid prescriptions nationwide dropped by almost 9%, according to a report by IQVIA Institute for Human Data Science.[14]

As doctors began to heed the warnings and scaled back on prescribing opioids, some patients who had become addicted to their prescription opioid turned to heroin, and deaths from heroin overdoses began to rise in 2010.[15] As the demand for heroin started to rise, the illicit drug market found its footing in synthetic opioids like fentanyl. As a matter of economics, heroin is not the best black market solution. Heroin is made from opium, which comes from the resin of the opium poppy. Many semi-synthetic prescription opioids like hydrocodone and oxycodone are also produced by this process. The process of growing the opium poppy plant, harvesting the resin, and processing it into the final product makes heroin expensive, which in turn creates a profit margin that is less than desirable for illicit drug producers.

Conversely, fentanyl is purely synthetic, which means that it can be made by one person in a lab. George Marquardt is credited with being the first person in America to illegally synthesize fentanyl.[16] Stories about Marquardt describe him as a genius, self-taught chemist who was also a high school dropout. Marquardt began to make heroin in his parent's basement when he was just 15 years old. Marquardt flooded the East Coast with illegally synthesized fentanyl and was eventually sentenced to 25 years in prison. At the time of his arrest in 1993, authorities linked at least 126 deaths to his product.

Fentanyl is 50 times more potent than heroin and 100 times more potent than morphine.

Illegally manufactured fentanyl is easier to produce and more profitable than heroin and is also driving the spike in overdose deaths. According to the CDC, drug seizures of fentanyl rose 426% from 2013 to 2014. During this same period, deaths involving synthetic opioids rose by 79%.[17]

Fentanyl is 50 times more potent than heroin and 100 times more potent than morphine. Even more alarming, however, is the fact that there are compounds with molecular structures closely similar to fentanyl (analogues) that are drastically more potent and these are now making their way into the hands of drug addicts. Carfentanil, a legal Schedule II controlled substance normally used as an elephant tranquilizer, is 100 times more potent than fentanyl and has been linked to spikes in overdoses in the Midwest.[18]

The CDC released a report in July of 2018 indicating that illicitly manufactured fentanyl is the "primary driver of recent increases in synthetic opioid deaths." The CDC reported in its *Notes from the Field* dated June 2018 that "during July 2016 - June 2017, among 11,045 opioid overdose deaths, 2,275 (20.6%) decedents tested positive for any fentanyl analogue, and 1,236 (11.2%) tested positive for carfentanil."[20]

FDA APPROVES NEW OPIOID 10 TIMES STRONGER THAN FENTANYL

As this research paper goes to publication, the Food and Drug Administration (FDA) has just announced that it has approved a new opioid marketed as DSUVIA, which is indicated for a sublingual tablet formulation of sufentanil, which is 10 times more potent than fentanyl. Dr. Raeford Brown, chair of the FDA advisory panel that approved the new drug, actually opposed the approval as did four U.S. senators citing concern about the safety of this new drug. Scott Gottlieb, FDA Commissioner, addressed these concerns in a statement released on November 2, 2018, in which he stated that Dsuvia will have strong limitations on its use, including the fact that it will not be available in retail pharmacies and is not available for patients to take home.

LETHAL DOSES OF FENTANYL AND CARFENTANIL RELATIVE TO A LETHAL DOSE OF HEROIN

A powerful image of the potency of fentanyl and carfentanil when compared to a lethal dose of heroin.

Figure 1: Illustration of relative lethal doses of heroin, carfentanil, and fentanyl[19]

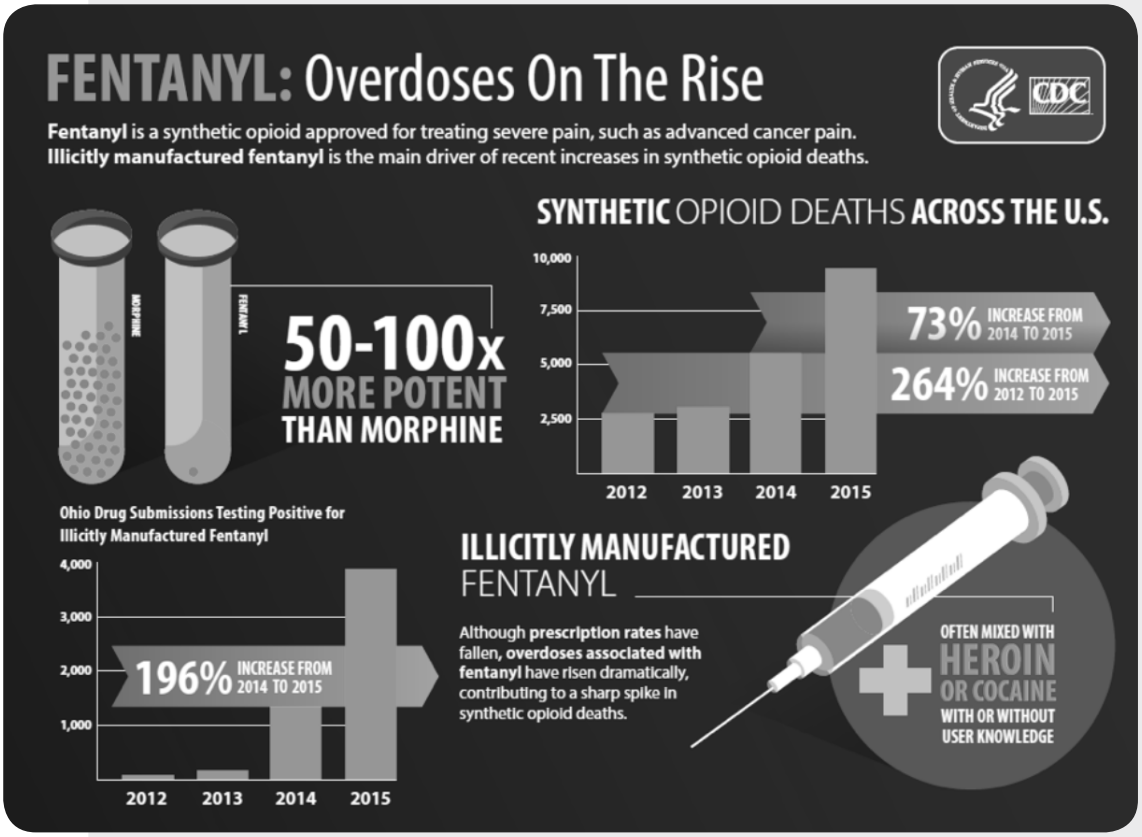

Figure 2: CDC Illustration of Overdoses Attributed to Fentanyl[21]

Fentanyl analogues are essentially structural variants of fentanyl. The modification of the chemical structure of a substance changes the identity of the substance but does not necessarily change its function. Currently, there are only four fentanyl analogues legal for medical use (i.e. Schedule II) including carfentanil (only veterinary use), sufentanil, alfentanil and remifentanil. All other analogues of fentanyl are Schedule I under the Controlled Substances Act (CSA).

The CSA classifies substances based on their chemical identity. For this reason, illicit manufacturers of fentanyl make analogues of fentanyl in an attempt to circumvent the regulations of the CSA. If the fentanyl analogue is not on the CSA list as an identified controlled substance, then it is technically not an illegal substance. At one time, illicit manufacturers were creating new forms of fentanyl faster than the DEA could identify and add them to the CSA list of Schedule I controlled substances. In June 2017, the DEA identified 230 instances of fentanyl or fentanyl-related substances or other synthetic opioids in drug seizures of illegal operations (see Figure 3, p.10). However, in November 2017, the DEA issued an emergency scheduling of all forms of fentanyl analogues declaring that "anyone who possesses, imports, distributes or manufactures any illicit fentanyl analogue will be subject to criminal prosecution in the same manner as for fentanyl and other controlled substances".[22]

As the demand for heroin started to rise, the illicit drug market found its footing in synthetic opioids like fentanyl.

Figure 3: The DEA's Analysis of Substances Identified in Drug Seizures in Q1 of 2017 Showing the Emergence of Fentanyl Analogues[23]

IN JUNE 2017, THE DEA IDENTIFIED 230 INSTANCES OF FENTANYL OR FENTANYL-RELATED SUBSTANCES OR OTHER SYNTHETIC OPIOIDS IN DRUG SEIZURES OF ILLEGAL OPERATIONS.

(SEE FIGURE 3)

According to a report by the U.S.-China Economic and Security Review Commission (USCC.gov), China is the primary source of illicit fentanyl flooding the streets of America because China's vast chemical and pharmaceutical industries are weakly regulated and poorly monitored.[24] Illicit fentanyl products make their way to the U.S. by direct shipment from China or indirectly through Mexico or Canada.

Carfentanil, a legal Schedule II controlled substance normally used as an elephant tranquilizer, is 100 times more potent than fentanyl and has been linked to spikes in overdoses in the Midwest.

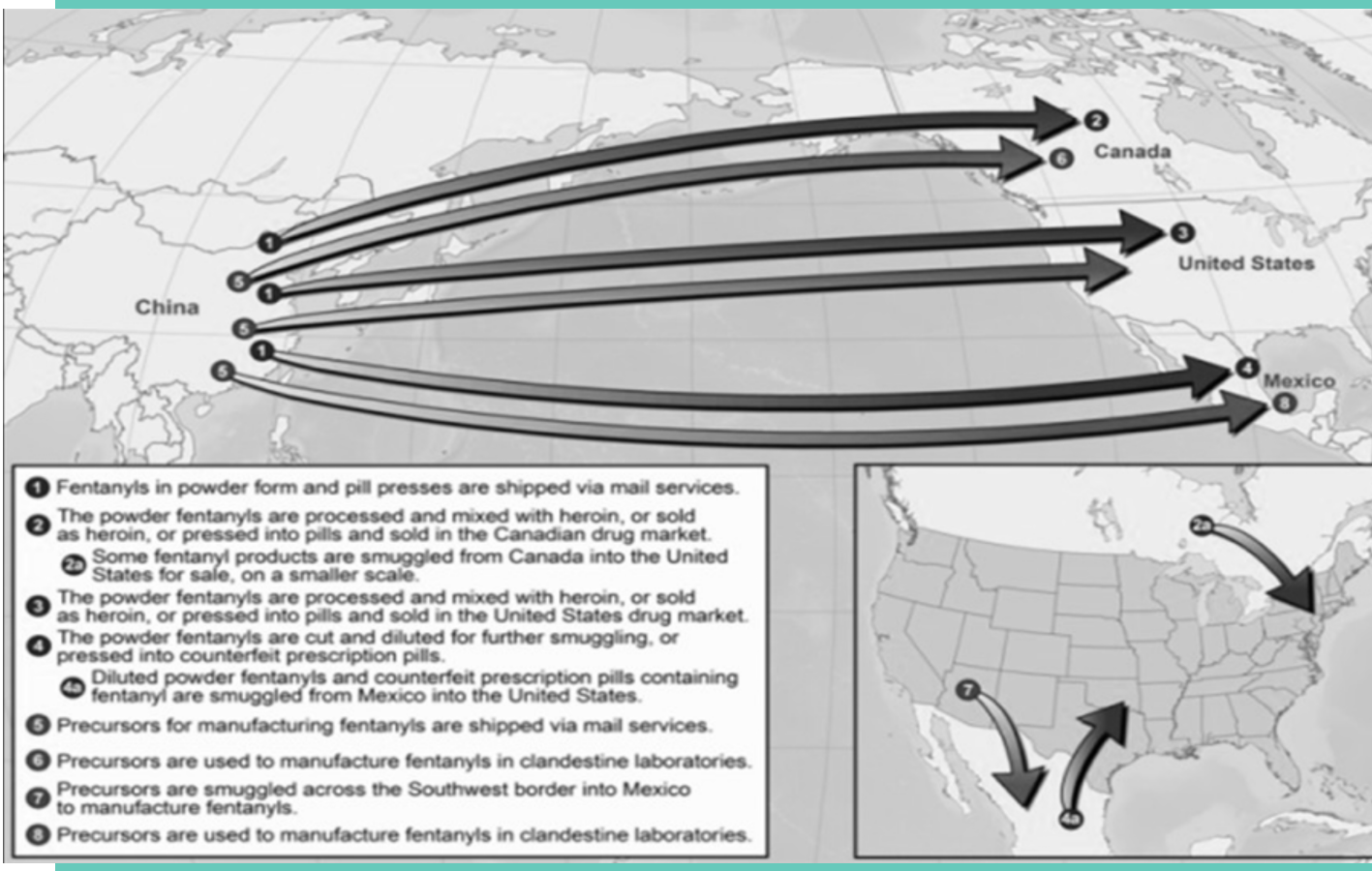

Figure 4: The DEA's Illustration of Fentanyl Smuggling Activity[25]

Figure 4 shows the ways in which illicit Fentanyl is infiltrating the addiction market:

1) Fentanyl is mixed with heroin

2) Disguised as heroin

3) Pressed and disguised as counterfeit prescription opioid pills.

The singer Prince died from an overdose linked to a counterfeit hydrocodone pill that actually contained fentanyl.[26]

WHAT DOES THIS MEAN FOR THE

WORKERS' COMPENSATION INDUSTRY?

Opioid use among injured patients has long been in the spotlight. Understandably, severe injuries may require the use of these powerful painkillers. It is a looming question though as to when legitimate medical use progresses to non-medical use--and to downright addiction. When a patient continues to take opioids long after the injury has resolved, the question becomes: does the patient actually need the medication or has the patient become addicted? The brutal truth is that addiction is very difficult to accurately identify and diagnose. Unless a patient admits to addiction, continual complaints of pain are often met with the continuation of opioid therapy, so there is a need for continual active patient management.

Not everyone who takes an opioid will become addicted, but addiction can come from anywhere. For this reason, any injured patient who is prescribed an opioid can be at risk of developing addiction and potentially be exposed to the illicit opioid market, which can lead to tragic consequences. With the presence of illicit fentanyl on the streets of America significantly heightening the threat of the ubiquitous illicit opioid market, clinical oversight is absolutely necessary to promote the appropriate prescribing of fentanyl-based prescription medications — and all opioids in general — to prevent the development of opioid addiction. Prescription fentanyl has a medical place in therapy for appropriately selected patients. Duragesic may be necessary for those experiencing severe chronic pain but who are unable to swallow solid dosage forms or have found other opioids to be ineffective. Additionally, if cancer has been diagnosed as a result of a work injury, even immediate-release fentanyl products may be required as long as they are prescribed appropriately.

The Official Disability Guidelines (ODG) state that Duragesic is "not recommended as a first-line therapy."[27] In regard to the immediate-release fentanyl products (e.g., Actiq, Fentora, Subsys, Lazanda, Abstral and Onsolis), use in musculoskeletal pain or chronic non-cancer pain is not recommended.[28] The *American College of Occupational and Environmental Medicine (ACOEM)* treatment guidelines provide similar recommendations for fentanyl, stating that Duragesic is "not recommended for routine use to manage chronic pain," and "immediate release/rapid-acting fentanyl is not recommended for treatment of sub-acute or chronic pain."[29]

Duragesic is not recommended for first-line therapy or routine use to manage chronic pain.

Recommendations for fentanyl as prescribed by some state-specific treatment guidelines:

CALIFORNIA Consistent with ODG

COLORADO[30]

Fentanyl is not generally recommended for use with musculoskeletal chronic pain patients. It has been associated with a number of deaths and has high addiction potential. Fentanyl should never be used transbuccally in this population.

MINNESOTA[31]

Exercise extreme caution when considering fentanyl therapy for pain, given the potential for diversion and harm. Clinicians trained or experienced with dosing and absorption properties of transdermal fentanyl are best equipped to prescribe, educate and monitor patients appropriately.

MONTANA[32]

Fentanyl is not generally recommended for use with musculoskeletal chronic pain patients. It has been associated with a number of deaths and has high addiction potential. Fentanyl should never be used transbuccally in this population.

NEW YORK[33]

Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer.

continued WORKERS' COMPENSATION INDUSTRY

The appropriate prescribing of opioid therapy is ultimately the responsibility of the prescriber. Unfortunately, as we have seen in the news, many lack the necessary training and some do not follow established guidelines — sometimes with tragic results.[34] **Ostensibly, third-party stakeholders such as the payer and pharmacy benefits manager must rely on the judiciousness of the prescriber and on the faith that doctors will follow best practices such as:**

- **Screening patients for addiction before starting opioid therapy and continually throughout treatment**
- **Using urine drug screenings to monitor compliance**
- **Paying attention and reacting to aberrant behavior**
- **De-escalating or discontinuing therapy when necessary and**
- **Providing or referring patients to addiction treatment when the addiction is exposed**

But faith can only take one so far.

That is why a strong rapport with the treating physician, along with strong clinical oversight, is vital. We must understand that the physician's role as the direct treatment provider is the toughest one among all the stakeholders involved in the care of an injured patient. Their decisions could mean the life or death of a patient and their commitment to their patients should not be undermined. We must support and encourage doctors to use alternative therapies when appropriate and engage doctors in a professional manner when issues of patient safety become apparent.

At myMatrixx, our success in managing pharmacy benefits for injured patients has always relied on our clinical expertise, but moreover, it is in how we deliver and convey this expertise to providers that matters. Strong clinical oversight only results in positive outcomes when it is exercised in a constructive, diplomatic and professional manner. With this overarching philosophy, myMatrixx will continue our commitment to ensuring the safe and effective treatment and rehabilitation of the American workforce whose injuries affect us all.

Resources available to safeguard your injured patients:

- **Formulary restrictions and plan edits**
- **Monitoring of morphine equivalent dose (MED)**
- **Prescriber interventions**
- **Advanced Opioid Management℠ (AOM)**
- **myMatrixx® myDataSense℠**

Consult with your myMatrixx Clinical Account Executive to find out more about these programs and our entire suite of clinical pharmacy services.

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