ANOTHER YEAR, ANOTHER MILESTONE.
By the latest CDC tally, the year 2015 saw more than 33,000 opioid overdose deaths, two-thirds of which were attributed to prescription opioids.¹

More than ever these statistics crystalize the need to explore and develop alternative chronic pain therapies. Yet pharmaceutical R&D seems determined to continue introducing new opioid products to the market, and the Food and Drug Administration (FDA) remains willing to approve them. Thus far in 2017, we have already seen approvals for two new long-acting opioid products for treatment of severe pain, Arymo® ER (morphine sulfate) and Vantrela® ER (hydrocodone bitartrate), with additional products on the horizon.

MAKING OPIOIDS SAFER
It is true that a concerted effort is underway (for a variety of reasons, and not all of them altruistic) to make future opioid products safer. Many products either recently approved or undergoing clinical trials have been developed with a greater emphasis on reducing patient risk, through measures that include abuse-deterrent formulations, improved side effect profiles, and diminished addictive properties.

But “safer” is a term relative to the population to which it’s being applied. And in workers’ compensation – a patient population that is commonly managed with opioid therapy to treat pain associated with workplace injury – these newer opioid products have thus far been unable to demonstrate a significant safety benefit. Primarily, they do not address the underlying risks and drivers of misuse in workers’ compensation patient populations.

MISUSE VS ABUSE: DIFFERENT MOTIVATORS, METHODS
There are important differences characterizing the recreational abuse of prescription opioids when compared with the clinical misuse that can occur within workers’ compensation. It would be naïve to imply that recreational abuse doesn’t occur among workers’ compensation patients. But by and far, injured workers don’t initiate therapy with the intent to abuse. Instead patients may find themselves navigating a slippery slope as they increasingly rely on opioids to cope – with their pain, with depression, with the very difficult task of accepting that the injury they’ve incurred means that their life and their livelihood may never quite look the same.

This reliance can translate into misuse if a patient is using opioid medications in clinically inappropriate ways (e.g., for longer periods of time than recommended, or taking their opioid medications at higher dosages or more frequently than prescribed by their doctor). These methods of misuse often boil down to taking too many pills, too often, and for too long. Conversely, recreational abuse is often hallmarked by methods of use intended to enhance the high: crushing, grinding or otherwise manipulating pills in order to snort or inject the opioid product for faster absorption into the body.

These key differences come into play when evaluating the potential risks of current and future opioid products within the injured worker population.
ABUSE-DETERRENT OPIOIDS

THE PROMISE: Special formulations designed to deter abuse, most commonly featuring technologies that either physically prevent manipulation of the tablet or capsule (chewing, crushing, grinding or extraction), or reduce the euphoric effects of the opioid when such manipulation occurs.

BENEFIT IN WORKERS’ COMP? Thus far abuse-deterrent opioids have been unable to effectively address the underlying motivators and patterns of opioid misuse in workers’ compensation populations.

Vantrela® ER (hydrocodone bitartrate) extended-release tablets

Approved January 2017: For pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Formulated with properties intended to make the tablet more difficult to manipulate for misuse and abuse through oral, intranasal, and intravenous routes of administration.

CURRENTLY AVAILABLE PRODUCTS WITH ABUSE-DETERRENT LABELING:

OXYCONTIN® (OXYCODONE HCL)
EXTENDED-RELEASE TABLETS
Abuse-deterrent formulation approved 2010; resistant to crushing, breaking, dissolution

EMBEDA® (MORPHINESULFATE/ NALTREXONE HCL)
EXTENDED-RELEASE CAPSULES
Naltrexone is activated when pill is crushed to counter the opioid effects

MORPHABOND™ (MORPHINE SULFATE)
EXTENDED-RELEASE TABLETS
Resistant to cutting, crushing, breaking

XTAMPZA® ER (OXYCODONE)
EXTENDED-RELEASE CAPSULES
Less susceptible to effects of grinding, crushing and extraction vs IR oxycodone

ZOHYDRO® ER (HYDROCODONE BITARTRATE)
EXTENDED-RELEASE CAPSULES
BeadTek™ technology forms viscous gel when crushed or dissolved

HYSTREL® ER (HYDROCODONE BITARTRATE)
EXTENDED-RELEASE TABLETS
Expected to deter misuse via chewing, snorting, injection

TROXYCA® ER (HYDROCODONE HCL/ NALTREXONE HCL)
EXTENDED-RELEASE CAPSULES
Expected to reduce abuse when crushed and administered orally or snorted

Arymo® ER (morphine sulfate) extended-release tablets

Approved January 2017: For pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative options are inadequate. Originally formulated to be abuse-deterrent, the FDA decided that it cannot be concluded that Arymo ER has physical and chemical properties that are expected to reduce abuse via the oral route.

KP201/APAP (benzhydrocodone HCl/acetaminophen)

Investigational: For short-term management of acute pain; under priority review by the FDA. If approved, could become the first immediate-release hydrocodone combination product with abuse-deterrent properties.

NEW/NOTABLE:

Source: www.healthesystems.com/rxinformer
**NEW/NOTABLE:**

**TRV130 (oliceridine)**

**Investigational:** Intravenous analgesic that treats moderate-to-severe acute pain with a reduced frequency of opioid-related adverse effects (e.g., nausea, vomiting, hypoventilation) when compared to intravenous morphine. Granted breakthrough therapy status by the FDA in early 2016.

**CL-108 (promethazine/hydrocodone/acetaminophen)**

**Investigational combination product:** Bi-layered tablet of immediate-release promethazine and modified-release hydrocodone and acetaminophen, indicated for moderate-to-severe pain while preventing or reducing opioid-induced nausea and vomiting.

New Drug Application was accepted in June 2016.

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**“NON-ADDICTIVE” OPIOIDS**

**THE PROMISE:** Opioids with reduced euphoric effect can reduce the potential for patients to become physically dependent or addicted.

**BENEFIT IN WORKERS’ COMP?** These products may prove easier to wean or discontinue when opioids are no longer clinically appropriate. Over the long-term, reducing the risk for dependence or addiction has the potential to make a significant impact on rates of abuse, misuse and overdose.

**NKTR-181**

**Investigational:** A mu-opioid receptor agonist designed to reach the brain more slowly than existing opioids to diminish euphoria. This New Chemical Entity (NCE) completed phase 3 trials in patients with chronic low back pain.

**CR845**

**Investigational:** A kappa opioid receptor agonist that targets the site of injury without passing the blood-brain barrier, CR845 is being called a non-addictive opioid that induces potent analgesia and anti-inflammatory properties, without adverse effects such as constipation, respiratory depression, or euphoria. The IV formulation of CR845 is currently in phase 3 clinical trials for post-operative (acute) pain and the oral formulation is in phase 2 trials for chronic pain.

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**SAFER OPIOID FORMULATIONS**

Many opioid products are now being developed with a greater emphasis on improving patient safety, through measures that include abuse-deterrent formulations, improved side effect profiles, and diminished addictive properties. But in the workers’ compensation patient population, where opioids are frequently prescribed to manage pain associated with workplace injury, do these products adequately reduce the risk for adverse effects including dependence, addiction, and debilitating side effects?
CURRENT MARKET: ABUSE-DETERRENT OPIOIDS
To date, efforts to bring safer opioids to market have largely centered on abuse-deterrent formulations. The FDA defines abuse-deterrent opioids as having properties shown to meaningfully deter, though not fully prevent, abuse. By this definition, the clinical misuse that occurs more commonly in the workers’ comp population becomes an unaddressed issue, because abuse-deterrent opioids are developed with the recreational abuser in mind. Abuse-deterrent opioids commonly feature technologies that either physically prevent manipulation of the tablet or capsule (chewing, crushing, grinding or extraction), or reduce the euphoric effects of the opioid when such manipulation occurs. Currently there are no abuse-deterrent formulations that reduce or remove euphoria when a patient swallows more intact pills than were prescribed, more frequently than directed, or remains on therapy for longer than clinically necessary or beneficial.

FUTURE OPIOIDS
Will future opioids offer more promise in deterring misuse? Maybe – with a side of caution. Although current abuse-deterrent technologies don’t address oral misuse, it’s not out of the question that they eventually will. FDA guidance allows for technologies that could potentially deter oral misuse – such as formulations that trigger unpleasant effects if a higher-than-directed dosage is ingested, or specialized delivery systems that remove patient behavior from the equation.

Drug manufacturers are also exploring ways to preempt addiction, studying opioids with greatly diminished euphoric effects that are being dubbed “non-addictive” opioids (see inside spread). Whether these products successfully live up to this name – and more importantly, whether they provide any subsequent safety benefit within the injured worker patient population – will remain to be seen.

OPIOID SIDE EFFECTS
Even when misuse is not a factor, opioids pose significant health concerns. Opioids come with a host of side effects that negatively impact a patient’s quality of life, delay the course of recovery, and dramatically increase the cost of their medical care. Opioid-induced constipation (OIC), a common and potentially debilitating side effect associated with opioids, can double a patient’s healthcare costs in the first year following initiation of their opioid therapy due to factors that include increased physician office visits and hospital admissions.2

PROBLEM OR SOLUTION?
With all of the societal and healthcare damages inflicted by opioids, it feels unlikely that the most effective solution is … more opioids. Yet they are being positioned as at least a part of the solution. There are currently more than 20 bills proposed that, if passed, will require insurance coverage for abuse-deterrent formulations of opioids.3 Some workers’ compensation insurers are feeling the costly sting of these products without seeing a resultant benefit for their injured worker patients. Costs that could instead be allocated to other treatment modalities that go beyond pain management and more effectively treat the patient’s condition or injury.

The workers’ compensation industry has put forth enormous efforts to tackle the opioid problem, and finally with some measurable success, as opioid prescribing rates have begun to decline in recent years.4 So while future opioids may offer some potential improvements over older formulations, it is not surprising that our industry views them with extreme caution and trepidation. For those of us dedicated to the safe and effective care of injured workers, opioids remain the enemy, not the answer.

SEE OUR VP OF CLINICAL SERVICES, DR. SILVIA SACALIS, CO-PRESENT:
Lessons from Workers’ Comp: Mitigating Drug Therapy Risk and Reducing Opioid Use
Tuesday, April 18th 1:00 pm

REFERENCES:

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For all of these reasons, it seems to follow that opioids with improved side effect profiles could prove beneficial among the injured worker population, and there are products in development that promise these benefits (see inside spread). But their potential benefits must continue to be carefully weighed against the overall risks. While reducing a side effect such as nausea or vomiting could improve a patient’s quality of life, it fails to address concerns such as addiction, overdose, or workplace safety.

Another important consideration in the injured worker population is the impact of opioid side effects on workplace safety. Patients who continue opioid therapy upon their return to work may suffer sedation, dizziness, and impaired function, all of which can present risks in certain work environments and inhibit the ability to perform skilled tasks.

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<tr>
<th>OIC</th>
<th>NON-OIC</th>
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<td>23,631 (± 67,209)</td>
<td>12,652 (± 19,525)</td>
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*Nonelderly patients with noncancer pain receiving opioid therapy >90 days