Zohydro® ER: To be or not to be?

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Learning objectives:

- Recognize the impact of chronic pain.
- Outline the pathophysiology of pain.
- Review of treatment of chronic pain.
- Recognize the impact of abuse/misuse and identify the need for abuse deterrence.
- Explain abuse deterrence.
- Outline important points of Zohydro ER®.
- Describe the controversy surrounding Zohydro ER®.
- Discuss some positive aspects of Zohydro ER®.
- Analyze the literature.
I. **Definition**

A. **Pain**
- Defined as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”
- In the practice setting: Whatever the patient says it is.

B. **Chronic pain**
- Usual acute pain is to alert the body that injury is present and needs to be taken care of.
- Persists with pain signals continuing to fire in the nervous system for weeks, months or even years.
- >3-6 months.

II. **Epidemiology**

- 1.5 billion people worldwide suffer from chronic pain.
- 3- 4.5% of the global population suffers from neuropathic pain, with incidence rates increasing with age.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Sufferers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>100 million</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.8 million</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>16.3 million</td>
</tr>
<tr>
<td>Cancer</td>
<td>11.9 million</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 million</td>
</tr>
</tbody>
</table>

*Table 1: Conditions in relation to chronic pain*

- Health care costs due to pain is $560 billion- $635 billion (2010) in the US.
- The most common types of pain are: back pain (27%), headache/migraine (15%), neck pain (15%) and face pain (4%).
- Average of 3.5 hours of lost productivity per week if pain is not adequately treated.

III. **Pathophysiology**

- Transduction: Noxious stimuli cause cell damage which causes an action potential.
- Transmission: Occurs in the dorsal horn of the spinal cord.
- Perception: Perceived by the brain.
- Modulation: Neurons from the brain stem release serotonin, norepinephrine and endogenous opioids to inhibit transmission and modulate pain.
- Chronic pain- Pain becomes disengaged from noxious stimuli or healing.
  - Abnormal CNS function.
  - Neuropathic pain.
IV. Treatment$^{2,3,4,5}$

A. Non-opioid agents

- Acute pain
  - Non-steroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen, ketorolac)
  - Acetaminophen (APAP)
- Chronic pain (adjuvants)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>TCA</td>
<td>10-50 mg at bedtime</td>
</tr>
<tr>
<td>Imipramine</td>
<td>TCA</td>
<td>same as amitriptyline</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>SNRI</td>
<td>75-225 mg/day (unlabeled)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>SNRI</td>
<td>60 mg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>AED</td>
<td>1200 mg in divided doses</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>AED</td>
<td>1800-3600 divided TID</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>AED</td>
<td>300-450 in divided doses</td>
</tr>
<tr>
<td>Lidocaine 5% patch</td>
<td>Local</td>
<td>Apply up to 3 patches at a time; patches may remain in place for up to 12 hours in any 24 h period</td>
</tr>
</tbody>
</table>

Table 2: Adjuvant treatment
B. Opioids
- Work on opioid receptors (mu, delta, kappa and sigma).
- Mu ~70% of opioid receptors.
- World Health Organization’s (WHO) pain ladder for cancer pain has been used as the standard for all types of pain in adults.

### Table 3: Weak opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>50-100 mg q4 h (IR) 100 mg daily</td>
<td>400 mg/day 300 mg/day</td>
</tr>
<tr>
<td>Codeine/APAP</td>
<td>15-60 mg q 4-6 h</td>
<td>Limited by APAP</td>
</tr>
<tr>
<td>Hydrocodone/APAP</td>
<td>2.5-10 mg q4-6 h</td>
<td>Limited by APAP</td>
</tr>
<tr>
<td>Oxycodone/APAP</td>
<td>2.5-10 mg q4-6h (IR) 10 mg q12 h (SR)</td>
<td>Limited by APAP</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>50 mg BID (ER)</td>
<td>500 mg/day</td>
</tr>
</tbody>
</table>

### Table 4: Strong opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg q 4 h (IR) 15 mg q12 h (SR)</td>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25 mcg/h patch q 72h</td>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2.5-10 mg q4-6 h (IR) 10 mg q 12 h (ER)</td>
<td>80 mg unless tolerant</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2-4 mg q4-6h (IR) 8-64 mg q24 h (ER)</td>
<td>Patient characteristics 64 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5 -5 BID-TID</td>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5-15 mg q4-6 h (IR) 10 mg q 12 h (ER)</td>
<td>5-20 mg /dose 80 mg in tolerant pts</td>
</tr>
</tbody>
</table>
C. Trial of opioids for chronic pain if:
- Moderate-severe pain
- Pain impacts quality of life
- Benefits outweigh risks

90% of the time opioids have not proven helpful in chronic pain.

D. Prior to initiation for chronic pain (>90d):
- Assessment of pain, abuse potential, mental health
  - Opioid risk tool (ORT)- risk for addiction (DIRE, SOAPP-R, COMM)
  - CAGE- for alcohol/drug issues
  - PHQ-9 for severity of depression
- Informed consent
- Plan for management of pain
- Close monitoring including urine drug tests.

V. Opioid abuse and misuse
6, 7, 8
A. Epidemiology in the US
- 4 million and 56 million patients receive extended release (ER) and immediate release (IR) opioids per year.
- 113 people die daily due to drug overdose and another 6748 patients are treated in the emergency room.
- The most common drugs involved in overdose are pharmaceuticals (55%) out of which the main class that was abused was opioids (74%).

B. Definitions related to abuse
- Tolerance: reduced drug effect over time due to exposure to the drug. This results in requiring increased doses to achieve the same degree of analgesia
- Physical dependence- results in withdrawal symptoms when the dose is abruptly reduced or discontinued or upon administration of an opioid antagonist.

  Tolerance and Dependence are not equivalent to addiction BUT are LIKELY to develop with chronic opioid use.

- Addiction: results in loss of control over drug use, compulsive drug use and use of the drug despite harmful effects.
- Abuse: “The intentional self-administration of a medication for non-medical purposes like altering ones state of consciousness.”
- Misuse: “use of medication for a medical purpose other than as directed, whether willful or unintentional, and whether harm results or not.”
- Tampering: a chemical or physical manipulation that changes or damages the integrity of the dosage form.
C. Drug seeking behaviors
- Using multiple doctors and pharmacies.
- Escalating the dose without provider input.
- Refilling prescriptions early.
- Claiming to have lost prescriptions.
- Not following up on any therapy other than opioids.

D. Differences in methods of abuse
- Ingestion is the most common route of abuse.

![Figure 3: Routes of administration of abused prescription opioids](image)

- From 1992-2002 injecting opioids decreased from 25-11% but oral abuse increased from 66-77%; snorting increased from 3-8%.
- Inexperienced abusers are most likely to use the oral route while more experienced abusers progress to intravenous and intranasal routes.

E. Ways to reduce drug abuse/misuse
- Prescription drug monitoring systems.
- Educating providers to change prescriber behavior.
- Convenient and cost effective disposal options.
- Public education.
- Abuse deterrence technology.

VI. Abuse deterrence
- Improving science and technology to prevent abuse before the drug hits the market in order to reduce the likelihood that the drug can even be abused.

A. Need for abuse deterrence
Individuals achieve a “rapid high” from prescription medications by taking excess orally, or crushing the pills and snorting/smoking or injecting the new formulation.
- This is due to the rapid peak serum concentration (Cmax) that is achieved in a short amount of time (Tmax).
- ER products are more attractive as when crushed, more of the drug is released at one time.
- Each opioid should be measured for its abuse quotient \( \text{AQ} = \frac{\text{Cmax}}{\text{Tmax}} \).
- Higher the AQ, higher the potential that the drug will be abused.

**B. Studies for abuse deterrence**
Abuse deterrent formulations need 4 categories of studies to be conducted for assessment per the FDA.
- Category 1: Laboratory manipulation and extraction studies \( \text{in vitro} \).
  - Goal: to evaluate which potentially abuse deterrent formulations can be defeated.
- Category 2: Pharmacokinetic studies.
  - Goal: Understand the \text{in vivo} properties by comparing PK profile of the manipulated drug to the intact formulation. Also comparing both of the above formulations with comparator drugs through one or more routes of administration.
- Category 3: Clinical abuse potential studies.
  - Goal: Assess the relative abuse potential of a new drug for purposes of scheduling under the Controlled Substance Act.
  - “Gold standard” is to compare the abuse liability of a new opioid to the abuse liability of a known opioid in volunteers with a history of previous drug abuse. If trial shows low abuse potential in this population, it is considered to have low abuse potential in the general population.
- Category 4: Post marketing studies.
  - Goal: To determine if the abuse deterrent formulation results in decreased abuse compared to formulations without abuse deterrence.

**Goal of abuse deterrence: to prevent abuse via intravenous and intranasal route along with oral ingestion.**

**C. Table 5: Current abuse deterrent drugs:**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic</th>
<th>Mechanism</th>
<th>Abuse deterrent labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboxone®</td>
<td>Buprenorphine/naloxone</td>
<td>Agonist/antagonist</td>
<td>NO</td>
</tr>
<tr>
<td>Opana ER®</td>
<td>Oxymorphone</td>
<td>Physical (INTAC)</td>
<td>NO</td>
</tr>
<tr>
<td>Exalgo®</td>
<td>Hydromorphone ER</td>
<td>Physical (OROS)</td>
<td>NO</td>
</tr>
<tr>
<td>OxyContin®</td>
<td>Oxycodone ER</td>
<td>Physical</td>
<td>YES</td>
</tr>
<tr>
<td>Talwin NX®</td>
<td>Pentazocine/ naloxone</td>
<td>Agonist/antagonist</td>
<td>NO</td>
</tr>
<tr>
<td>Embeda®</td>
<td>Morphine/naltrexone</td>
<td>Agonist/antagonist</td>
<td>NO</td>
</tr>
<tr>
<td>Ultram ER®</td>
<td>Tramadol</td>
<td>Physical</td>
<td>NO</td>
</tr>
<tr>
<td>Targiniq ER®</td>
<td>Oxycodone/naloxone</td>
<td>Agonist/antagonist</td>
<td>YES</td>
</tr>
</tbody>
</table>
D. Abuse deterrence mechanisms

1. Physical barriers: change physical form of oral drug making it more difficult to abuse by chewing, crushing, cutting, grating or grinding.
   a. Solid formation- insoluble in a certain medium or cannot be crushed or chewed (cannot reduce particle size).
      i. Ex: OxyContin ®- resists crushing and chewing. If crushed- makes a viscous solution with water making it impossible to inject.
   b. Gel formation- viscous or semi-solid formulations. Either viscous to begin with or become viscous when mixed with a solvent. Thus they cannot be abused by injecting.
   c. Non intentional- Drug not originally formulated as abuse deterrent but are found to be less abused due to their technology.
      i. Ex: Concerta ® - formulated using osmotic controlled delivery system (OROS) - the inner core has the medication while the outer layer is made of high molecular weight polymers that make it rigid. Controlled release of the drug occurs through a small laser drilled hole in the rigid outer layer. If tried to crush or gain access to the drug, it forms irregular fragments that form a gel in solution preventing abuse by inhalation and injection.

2. Chemical barriers: Add a chemical substance or perform a chemical modification on an abused drug.
   a. Aversive agent- substances added to the formulation to produce an unpleasant effect if abused or overdosed.
      i. Ex: Lomotil ®- atropine is added to diphenoxylate to deter abuse as it will cause weakness and fatigue if used in excess.
   b. Agonist/Antagonist combination- Naloxone when given orally has no pharmacological effect as it goes through extensive first pass metabolism. It is, however, very effective when given IV.
      i. Ex: Suboxone ®- available as sublingual (SL) film and tablet. Film was designed to deter abuse by inhalation. Thus if it is tried to be abused by injection, naloxone is activated and the patient goes through withdrawal.
   c. Metabolic pathway- Using a prodrug (conversion to active form requires biologic metabolic process).
      i. Ex: Vyvanse ®- after oral administration, prodrug is metabolized to its active dextroamphetamine. If injected or inhaled, there is not a quick rise in the levels of the medication.


VII. Zohydro ER® (hydrocodone ER)¹¹,¹³
   - Semisynthetic opioid agonist that acts on the mu receptors
- **Indication:** Is 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.”

- **Dosing:** Start with 10 mg q12h and titrate up in increments of 10 mg every 12 hours every 3-7 days as needed to achieve analgesia.

- **Boxed warning:** Zohydro ER® exposes users to risks of addiction, abuse and misuse which can lead to overdose and death. Assess each patient’s risk before prescribing and monitor regularly for development of these behaviors or conditions.

- **Zohydro ER®** uses Spheroidal Oral Drug Absorption System (SODAS) technology.
  a. After dissolution of hard gelatin layer, gastrointestinal fluid enters the beads and solubilizes the drug.
  b. After dissolving, the active medication may diffuse out of the beads at a predetermined rate.
  c. This allows for both immediate and time-release of hydrocodone for twice daily dosing.

- **Cost:** Depends on the strength-
  - Hydrocodone ER
  - Hydrocodone/APAP
  - 10 mg (100): $702.
  - 50 mg (100): $858.
  - 5/325 (100): $54.20.
  - 10/325 (100): $70.20.

- **Table 6: Conversion from other opioids to hydrocodone ER:** (NOT equianalgesic)

<table>
<thead>
<tr>
<th>Prior opioid</th>
<th>Oral dose (mg)</th>
<th>Approximate oral conversion factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3.75</td>
<td>2.67</td>
</tr>
<tr>
<td>Morphine</td>
<td>15</td>
<td>0.67</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- Table can only be used for conversion FROM current opioids TO Zohydro ER®.

VIII. **Controversy**^{12,13}:
- Zohydro ER® can be easily abused by ingestion, crushing, sniffing or injection. The SODAS technology is not tamper resistant.
- The FDA approved the medication in October 2013 despite an 11-2 vote against approval by the advisory board.
- The attorney generals of 29 states sent the FDA a letter asking them to revoke the decision as they thought it would exacerbate the already prevalent problem of prescription drug abuse.
IX. Positive aspects of Zohydro ER®[^12]:
- Can serve as an additional option to treat pain as people respond differently to different opioids.
- Provides a non-acetaminophen option and can reduce the incidence of acute liver failure.
- Provides 12 h dosing and steadier blood levels.
They also argued that they were including a number of initiatives to reduce the misuse and abuse and were working on developing an abuse deterrent formulation.
- Locking bottle caps or a lock box that can be bought with a coupon when prescribed Zohydro ER®.
- The FDA is also requiring certain safety parameters from the manufacturers:
  - The FDA requires the manufacturer to participate in the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS).
  - The FDA also requires the company to conduct post marketing studies to assess the risks of misuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death associated chronic use.

X. Summary:
- While these are positive aspects, the FDA recently made all formulations containing hydrocodone a schedule II to reduce misuse and abuse.
- On one hand they approve a medication like Zohydro ER® and on the other are trying to reduce the effects of prescription drug abuse.

XI. Literature review[^14,^15,^16]

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate effects of physiochemical barriers to crushing and dissolving on safety outcomes associated with extended-release oxycodone (ERO) tablets (OxyContin) using a national surveillance system of poison centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>Purdue Pharma</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Decrease in number of phone calls to the poison center for ERO compared to single entity (SE) oxycodone due to therapeutic effects and accidental exposures.</td>
</tr>
</tbody>
</table>

[^12]: reference to the source of the information.

### Methods

- Information collected from National Poison Data System.
- Changes were compared from 1 year preceding (3Q2009-2Q2010) to the 2 years after reformulated ERO (4Q2010-3Q2012)
- Both original and reformulated ERO were used in the data.
- Classified into: Intentional abuse (exposure due to intentional, improper, or incorrect use in order to get high), unintentional therapeutic errors (unintentional deviation from proper regimen resulting in wrong dose, drug or incorrect administration), unintentional general errors (children accidentally swallowing medication), and adverse reactions.
- 1 year prior to ERO- baseline and change from baseline was calculated

### Results

- ERO exposures decreased compared to baseline with respect to all, abuse, therapeutic errors and accidental exposures.
- In contrast, the rate of all exposures either did not change or increased for single entity oxycodone.
- The rate of exposure to heroin increased especially post reformulation starting 4-6 months after reformulation showing preference of heroin over ERO.
- All exposures for ERO decreased 26% but increased 15% for SE oxycodone and 37% of heroin \( P < 0.0001 \).
- Intentional exposures decreased 25% but increased 17% for SE oxycodone \( P < 0.0001 \).
- Abuse exposures decreased 36% for ERO and increased 20% for SE oxycodone \( P < 0.0001 \).
- Unintentional therapeutic errors for ERO decreased 20% and increased 19% for SE oxycodone \( P < 0.001 \).
- Unintentional general exposures decreased 39% for ERO and had no change in SE oxycodone and increased 21% for heroin.
- Majority (63%) of unintentional general exposures was children 1-2.5 years of age which decreased by 51% \( \text{CI: -60 to -40 %} \).
- Adverse reactions for ERO decreased 34% and increased 15% for SE oxycodone \( P 0.0005 \).
- Prescriptions for ERO decreased 2% in the first and 9% in the second year after reformulation whereas prescriptions for SE oxycodone increased 51% by 3Q2012.\( P. 16, 17\)-Appendix 1

### Authors conclusions

- Physiochemical barriers do decrease the rate of abuse and adverse events due to misuse.
- Development of abuse deterrent formulations is a public health priority.
- Combined with education and regulation to reduce the risks and improve benefits of opioid analgesics
Strengths
- National scale
- Break down of reason for reporting (abuse, unintentional exposure etc.)
- Comparison to heroin
- Time frame

Weaknesses
- Unable to differentiate between original and reformulated ERO
- Underestimated impact of reformulation
- Other possible reasons for decrease: changes in reporting, reduction in ERO prescriptions; prescription adjusted analyses were conducted.
- Funding bias

My conclusion
- The rate of ERO exposure did decrease but seems to have shifted over to heroin.
- Education and regulation need to be combined to reduce the risks of opioids.

Sessler et al. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse deterrent formulation. *Pharmacoepidemiology and Drug Safety*. 2014; wileyonlinelibrary.com

<table>
<thead>
<tr>
<th>Objective</th>
<th>Impact of reformulated ERO based on reports of fatalities submitted to the manufacturer’s pharmacovigilance database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>Purdue Pharma</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Ratio of ERO deaths vs all deaths related to oxycodone reported on FDAs Adverse Event Reporting System (AERS).</td>
</tr>
</tbody>
</table>

Methods
- Reports were classified as opioid overdose event and/or drug abuse related behavior
- Reports that lacked a core reporting element (patient, reported, drug etc.) or involved in litigation were excluded.
- Search manufacturers data base for adverse events related to ERO from 3Q2009-3Q2013 (1 year before to 3 years after)
- Fatalities divided into 4 periods:
  - 1 year before (3Q2009-2Q2010)
  - 1 year after (3Q2010-2Q2011)
  - 2 years after (3Q2011-2Q2012)
  - 3 years after (3Q2012-2Q2013)
- Fatalities reported by health professionals were assessed separately as accuracy would vary.

Results
- 326 fatalities involving ERO were reported to the manufacturer in this time period.
- Abuse related behavior was mentioned in 206 reports.
- Overdose was mentioned in 240 reports.
- Reports involving fatal overdoses were most reported by health care professionals and mostly involved adults (18-64 yo) and
polysubstance use.
- There was decrease in the proportion of fatality reports from southern regions (40-29%) and those with benzodiazepines (42-33%) or other opioids (37-24%)
- Fatalities decreased post reformulation with a slight increase for the first year post reformulation.
- Fatalities decreased 82% (CI: -89 to -73%) from the first to third year post reformulation.
- Fatalities involving overdose decreased 87% (CI: -93 to -75%) from the first to third year post reformulation.
- Number of ERO prescriptions decreased post reformulation.
  - The prescription adjusted rate of all fatality reports decreased by 80% (CI: -87 to -67%)
- Changes were not significant in the first year post formulation but were significant starting year 2.
- An increase in adverse events appeared shortly after reformulation within 3 months of the new drug being marketed.
  - A survey of 1967 subjects showed that 93% of adverse events were from patients who have used ERO for some time and were reporting changes from what they were used to.
- Ratio of number of fatalities decreased from 21% to 22%, 8%, and 10% in the first, second, and first six months of third year post reformulation respectively. *(P. 17,18- Appendix 2)*

| Authors conclusions | - Fatalities decreased after introduction of ERO-especially overdose and abuse
|                     | - Non-fatal reports involving ERO remain unchanged.
|                     | - Combined with education and regulation to reduce the risks and improve benefits of opioid analgesics |
| Strengths           | - Time period
|                     | - Differentiating between abuse and overdose. |
| Weaknesses          | - Possibly due to reduction in ERO prescriptions- did include prescription adjusted analysis
|                     | - Funding bias
<p>|                     | - Included both original and reformulated ERO. |
| My conclusion       | - Abuse deterrent properties did decrease fatalities but education and regulation is still important to reduce abuse and overdose. |</p>
<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To characterize the abuse deterrent properties of oxycodone/naloxone solution and evaluate pharmacokinetic, pharmacodynamic, safety, tolerability and abuse parameters of IV oxycodone/naloxone in an opioid-experienced, nonphysically dependent population</th>
</tr>
</thead>
</table>
| **Enrollment** | - N= 24  
- 34.9 years  
- 87.5% male  
- 87.5% white  
- 22 completed the study |
| **Funding** | Funded by Purdue Pharma |
| **Trial design** | Single center, double blind, randomized, placebo controlled, cross over study |
| **Inclusion criteria** | - 18-55 years  
- Nondependent recreational users with multiple (≥2) routes of administration  
- BMI 18-29.9 with minimum weight of 50 kg  
- Must have taken 40 mg of oxycodone at least once in lifetime  
- Negative urine drug test  
- Negative breath alcohol tests |
| **Exclusion criteria** | - Symptoms of withdrawal  
- Dependence in the past 2 years  
- Participation in a rehabilitation program  
- Use of >20 cigarettes/ day  
- No medications were permitted except APAP (<2 g/d), vitamins, birth control within 7 days of first dose. |
| **Outcomes** | Abuse potential, safety and tolerability of IV administration of oxycodone/naloxone |
| **Methods** | Four phase study:  
- Screening- confirm patients had moderate experience with opioid abuse but were not physically dependent (pass a naloxone challenge test).  
- Qualification- if patients could differentiate between oxycodone and placebo followed by a 24 hour washout period.  
- Treatment- Patients received 0.07mg/kg oxycodone, 0.07 mg/kg oxycodone and 0.035 mg/kg naloxone solution or just placebo over 3 visits.  
- Follow up- Patients returned for one visit 3-7 days after last administration  
- 100-points VAS to quantify treatment effects  
- Subjective drug value was determined by asking patients to make a choice between receiving another dose of sOXN or specified amount of money ($0.25-$50). |
**Results**

- Overall drug liking was lower for placebo and sOXN compared to OXY.
- Good effects, high and take drug again were also higher for OXY compared to sOXN and placebo.
- Pairwise comparisons were significant for OXY vs. sOXN (p<0.01) and OXY vs. placebo (P<.001) but not significant for sOXN vs. placebo.
- Adverse events were the highest for OXY (95.7%), then sOXN (29.2%) and least for placebo (20.8%).
- The most common adverse events were euphoric mood, feeling hot, somnolence and headache.
- 1 subject discontinued because of a ventricular tachycardia following administration of placebo. *(P. 19, 20- Appendix 3)*

**Authors conclusion**

- sOXN is less appealing to drug users due to its abuse deterrent properties and might prevent the tablet formulation from being abused.
- Naloxone significantly reduces but does not eliminate the central effects of oxycodone when given intravenously.

**Strengths**

- Design
- Followed the FDA rules for abuse deterrence.

**Weaknesses**

- In the real world- higher doses of abuse (not in 2:1 ratio)
- Funding bias
- Other factors: alcohol, other drugs etc.

**My conclusion**

- Naloxone helps to reduce abuse and misuse due to its unique properties
- Post marketing studies are needed to assess this in real world situations.

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**XII. Summary:**

- Zohydro ER ® will provide another option in the arsenal of long acting opioid medications for chronic pain.
- Abuse deterrence formulations would help in reducing the abuse and misuse of opioids through IV and intranasal routes.
- Further research needs to be done to prevent abuse by ingestion as that is the most frequent route used for abuse.
- Abuse deterrence has to be combined with education of health care professionals and regulations to combat abuse and misuse of opioids.
- Ultimately, as with all opioid medications in chronic use, patients should be assessed for risks of abuse/ misuse and closely monitored while on therapy.
- Looking into the future: Zogenix is working on two new abuse deterrent formulations for hydrocodone ER.

**References:**


Appendix 1:
Coplan et.al. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse deterrence characteristics.

Figure 4
Appendix 2:
Sessler et al. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse deterrent formulation.
Appendix 3:
Colucci et. Al. Abuse Potential of Intravenous Oxycodone/Naloxone Solution in Nondependent Recreational Drug Users
Figure 9

Table 1 Summary of VAS scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>$E_{\text{max}}$</th>
<th>$p$ value from pairwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OXY</td>
<td>sOXN</td>
<td>Placebo</td>
</tr>
<tr>
<td>Overall Drug Liking$^a$</td>
<td>79.5 (26.7)</td>
<td>49.5 (18.5)</td>
<td>46.0 (15.0)</td>
</tr>
<tr>
<td>Take Drug Again$^a$</td>
<td>82.0 (28.4)</td>
<td>37.0 (29.0)</td>
<td>34.5 (24.2)</td>
</tr>
<tr>
<td>Good Effects</td>
<td>94.0 (21.2)</td>
<td>20.0 (34.9)</td>
<td>2.7 (11.7)</td>
</tr>
<tr>
<td>High</td>
<td>94.6 (21.3)</td>
<td>19.6 (33.4)</td>
<td>2.9 (11.7)</td>
</tr>
<tr>
<td>Bad Effects$^b$</td>
<td>11.5 (22.4)</td>
<td>7.5 (21.2)</td>
<td>2.9 (12.3)</td>
</tr>
<tr>
<td>Feeling Sick$^b$</td>
<td>10.3 (23.0)</td>
<td>7.5 (23.2)</td>
<td>3.0 (10.8)</td>
</tr>
<tr>
<td>Drowsiness/Alertness$^c$</td>
<td>32.1 (25.1)</td>
<td>47.3 (23.4)</td>
<td>47.2 (25.0)</td>
</tr>
</tbody>
</table>

Figure 10

Figure 11

Fig. 4 End-of-treatment balance measures, administered at 8 h post-dose (n = 22). Bars indicate mean (SD) of each measure. For Overall Drug Liking VAS (left panel), Take Drug Again VAS (center panel), and Subjective Drug Value (right panel), $p < 0.001$ for OXY vs both sOXN and placebo; sOXN simulated oxycodone/naloxone, OXY oxycodone, VAS visual analog scale, SD standard deviation.