

Session 334: I Want a New Drug: Novel Uses for Old Friends

Program Title: Coming Soon to Your Neighborhood: Zohydro, Fentanyl Spray, Prescription Naloxone, and Lots of Buprenorphine

Session Overview

It's tough to keep up with all of the new drugs that hit the market each year. This session will focus on four medications in the opioid family that, although they've been around for a while, have new formulations available. Particular emphasis will be placed on what the ED provider needs to know about these drugs.

Objectives

- Explain the backlash surrounding the approval of extended-release hydrocodone in 2013.
 - Describe the potential expanded role of naloxone in the community to help prevent opioid overdose deaths.
 - Given an ED patient on buprenorphine, outline an approach to managing acute pain.
1. Hydrocodone (Zohydro® ER)
 - a. Zohydro is the first hydrocodone-only product to become available in non-liquid form. (<http://zohydroer.com/hcp/>)
 - b. It was approved in 2013 with a tremendous amount of backlash (ongoing).
 - i. Prior to its approval, an FDA advisory panel voted 11-2 not to approve the drug.
 - ii. It has no deterrent (tamper-resistant) technology.
 - iii. Its approval came one day after FDA decision to 'upschedule' hydrocodone from a Schedule III to Schedule II controlled substance
 - iv. In the fight against the opioid epidemic, this new drug appears to only further the problem. Drs. Lewis Nelson, David Juurlink, and Jeanmarie Perrone published a critical article on FDA's decision (*Expert Opin Drug Saf* 2014;13(4):407-10).
 - v. Governor Deval Patrick of Massachusetts banned Zohydro® ER in his state in March 2014 and declared a public health emergency in response to the state's growing opioid addiction epidemic. But in April, US District Court Judge Rya W. Zobel struck down the ban, saying the state lacked the authority to override the FDA's approval of the painkiller. (<http://www.bostonglobe.com/metro/2014/04/15/federal-judge-says-patrick-administration-cannot-block-sale-painkiller-zohydro-massachusetts/DILlz9qETePxqC29Ob27CN/story.html>)
 - vi. The FDA defends its decision to approve this drug by saying that millions of people can potentially benefit from its use FDA Commissioner Margaret Hamburg explains in her blog: "We have heard from many people who must cope with often severe pain on a daily basis. These are people who need a

variety of therapies to have any hope for a quality life. And, importantly, Zohydro does not include the liver toxin acetaminophen, as many hydrocodone products (e.g., Vicodin) do.” She also states, “**And this drug is unlikely to increase the number of people abusing opioids.**”

<http://blogs.fda.gov/fdavoce/index.php/2014/04/the-way-forward-on-opioid-abuse-a-call-to-action-for-science-based-comprehensive-strategies-2/>

- c. Zohydro[®] ER is available in 10-50 mg capsules to be administered every 12 hours.
 - d. If that wasn't enough, don't forget about the even newer hydrocodone product approved November 2014, Hysingla ER. At least this one has abuse-deterrent properties!
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm>
 - e. There really isn't much utility for these drugs by the ED practitioner. Neither drug contains acetaminophen. Effects from overdoses are expected to last longer than traditional hydrocodone products due to the extended-release nature of the products. Naloxone should be effective in reversing toxicity.
2. Fentanyl spray
 - a. A new fentanyl product (Subsys[®]) is a sublingual spray approved only for breakthrough pain (<http://subsyspray.com/>)
 - b. Strengths
 - i. 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
 - c. Subsys[®] is really meant for oncology patients already receiving around-the-clock opioids. They continue the around-the-clock treatment while taking Subsys[®] for breakthrough pain.
 - d. Subsys[®] starts to have an effect within 3-5 minutes and lasts about an hour.
 - e. Subsys[®] is part of the REMS program:
<https://www.tirfremssaccess.com/TirfUI/remss/home.action>
 - f. The drug is primarily used by oncologists for patients in the outpatient setting. An ED provider will not prescribe Subsys[®], but may encounter patients on it. For patients with acute pain presenting to the ED, the last dose of Subsys[®] should be noted as part of the pain management assessment.
 3. Naloxone
 - a. In the midst of an unprecedented opioid epidemic, there have been considerable efforts to expand access to naloxone. (Doyon S, et al. J Med Toxicol 2014;10:431-4)
 - i. Most naloxone administered by laypersons is prescribed and distributed as part of 'overdose education and naloxone distribution' or 'bystander naloxone training' programs
 - ii. Administration of naloxone by bystanders is reported in over a dozen feasibility studies with reversal rates ranging from 75 to 100 % of cases
 - b. Naloxone is labeled for IV/IM/SQ administration
 - i. Two strengths available 0.4 mg/mL and 1 mg/mL
 - ii. Three manufacturers
 1. Hospira

2. Mylan
 3. IMS/Amphastar – makes prefilled syringe
 - iii. Mucosal Atomization Device – LMA Ltd.
 1. 510k FDA approved nasal delivery device
 2. Luer-fitting for attachment to syringes
 - c. New product, Evzio™ is a hand held, prefilled 0.4 mg dose (with one repeat dose). Talks the person administering the drug through the process (kind of like an AED).
<http://evzio.com/hcp/>
 - d. Prescribing options
 - i. Naloxone vial and needle – traditional IM/SQ using 0.4 mg/mL injection vial and needles
 1. Least expensive - \$10-15
 2. FDA approved
 - ii. IMS/Amphastar 2 mg/mL Prefilled Syringe and Mucosal Atomization Device
 1. \$30-50/kit
 2. Products FDA approved but intranasal administration is off-label
 - iii. Evzio™ Autoinjector
 1. \$200-700 per Rx depending on insurance
 2. FDA approved in 2014
 - e. How to write the prescription
 - i. Intranasal
 1. Naloxone 2 mg/2 mL prefilled syringe, #2
 2. SIG: Spray one-half of syringe into each nostril upon signs of opioid overdose. Call 911. May repeat X 1.
 - ii. Intramuscular
 1. Naloxone 0.4 mg/mL single dose vial, #2
 2. SIG: Inject 1 mL intramuscularly upon signs of opioid overdose. Call 911. May repeat X 1.
 - f. Additional resources
 - i. SAMSHA free publication: <http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit-Updated-2014/SMA14-4742>
 - ii. Prescribe to Prevent: <http://prescribetoprevent.org/>
 - iii. Stop Overdose: <http://stopoverdose.org/pharmacy.htm>
4. Buprenorphine
- a. There are 3 new products available containing buprenorphine
 - i. Bunavail™ buccal film (<http://www.bunavail.com/>)
 1. Strengths
 - a. Buprenorphine and naloxone 2.1/0.3 mg, 4.2 mg/0.7 mg, 6.3 mg/1 mg
 - ii. Zubsolv® sublingual tablets (<http://www.zubsolv.com/>)
 1. Strengths
 - a. Buprenorphine and naloxone 1.4 mg/0.36 mg , 5.7 mg/1.4 mg
 - iii. Suboxone® sublingual film (<http://www.suboxone.com/>)
 1. Strengths

- a. Buprenorphine and naloxone 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg
- b. The indications are the same as original Suboxone/Subutex, induction and maintenance treatment for opioid dependence
- c. In theory, the new formulations allow for easier administration and more consistent absorption.
- d. They all still contain the naloxone component to deter abuse.
- e. Pharmacology (Heit HA, et al. *Clin J Pain* 2008;24(2):93-7. & Jones HE. *Sci Pract Perspect* 2004;2(2):4-20.)
 - i. Buprenorphine is a partial agonist at the mu-receptor. What this means is that buprenorphine binds to the same receptor as a full agonist, such as morphine, but does not stimulate the receptor as strongly. The classic mu-receptor effects of pain relief, euphoria, and respiratory depression will be less with a partial agonist.
 - ii. Buprenorphine has very high affinity for the mu-receptor—one of the highest of all the opioids. This means that any other opioid occupying the mu-receptor will be kicked off and replaced by buprenorphine. Thinking clinically, if a patient used heroin (a full agonist) and then was administered buprenorphine (a partial agonist), the patient would experience withdrawal signs and symptoms. The buprenorphine has a higher affinity than heroin and will replace it at the receptor, providing only partial stimulation.
- f. Buprenorphine and Acute Pain Management: The ED Perspective (<http://www.aliem.com/buprenorphine-acute-pain-management/>)
 - i. Non-opioid options should first be considered in patients on buprenorphine presenting with acute pain. Some would argue that if the pain is severe enough to require opioids, the patient probably should be admitted. If it is determined that a patient absolutely must have a short course of opioid therapy, there are several options to manage this complex situation depending on the anticipated duration of pain, treatment setting, and response to therapy. However, only one approach is potentially feasible for the ED provider caring for a patient who will be discharged: **Continue buprenorphine maintenance therapy and titrate short-acting opioid analgesics.** (Alford DP, et al. *Ann Intern Med* 2006;144(2):127-34).
 1. Expect that a higher dose of opioid will be needed. More is required to compete with and overcome the high affinity of buprenorphine for the mu-receptor. We must be cognizant that this is a slippery slope. Expert consultation is advised and follow up should be soon. Instead of the usual oxycodone 5 or 10 mg every 4-6 hours, 15 or 20 mg may be needed. PO hydromorphone may be another option. The shortest course feasible should be prescribed. If a patient were to stop taking their buprenorphine, its effects would wear off after 24-48 hours. A

patient continuing to take a higher opioid dose could experience respiratory and CNS depression without the buprenorphine present to compete for the mu-receptor.

2. Do not use combination products with acetaminophen. The 4 gram daily limit will quickly be exceeded if the patient needs 15 or 20 mg of oxycodone every 4-6 hours. The patient may use acetaminophen concomitantly as a separate product, but be sure to educate them.
 3. Arrange follow-up with the patient's primary care provider and/or pain/addiction specialist as soon as possible.
- g. Buprenorphine resources
- i. Substance Abuse and Mental Health Services Administration (SAMHSA):
<http://buprenorphine.samhsa.gov/index.html>
 - ii. Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) Risk Evaluation and Mitigation Strategies (REMS):
<https://www.btodrems.com/SitePages/MedicationGuides.aspx>
 - iii. What is REMS?
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>