Management of Pain in Pregnancy

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Disclosures

- Final disclosures: none
- Conflicts of interest: none
- Off-label use of Ketamine will be discussed
- Clinical disclosure: I am a full-time practicing anesthesiologist, but I do not specifically practice chronic pain or addiction medicine
- Special thanks to Dr. Jim Molnar and Dr. Ann Tuttle, who assisted me in preparing this lecture
Objectives

- Review methods to care for women with opioid dependence providing care that promotes healthy behaviors
- Increase awareness of non-narcotic options for treating pain in pregnant patients
Drug Overdose: An Epidemic in Ohio

- 2007: unintentional drug poisoning overtook MVA as leading cause of accidental death in Ohio
- 366% increase in rate of fatalities from 411 in 2000 to 1,914 in 2012
- Unintentional fatal drug overdoses cost Ohioans $2.0 Billion in 2012
- [http://www.healthy.ohio.gov/default.aspx](http://www.healthy.ohio.gov/default.aspx)
Guidance from the ODH

• Avoid starting long-term opioid therapy for chronic non-malignant pain
• Not obligated to prescribe opioids when a favorable risk-benefit balance cannot be documented
• First consider non-pharmacologic and non-narcotic approaches
• Exercise the same caution with Tramadol (Ultram) as with opiates
• Avoid co-administration of benzodiazepines
• Morphine Equivalent Daily Dose (MED) 80mg “Trigger Point”
Ohio Administrative Code
Chapter 4731

- "If the practitioner believes or has reason to believe that the patient is suffering from addiction or drug abuse, the practitioner shall immediately consult with an addiction medicine specialist or other substance abuse professional to obtain formal assessment of addiction or drug abuse."

- “To assist in this determination, the physician shall access OARRS....”
Reasons to suspect abuse/diversion (3741-11-11)

- Selling Rx drugs
- Forging/altering a Rx
- Stealing or borrowing reported drugs
- Increasing the dose of reported drugs in amounts that exceed the prescribed dose
- Drug screen inconsistent with treatment plan or refusal of drug screen
  • Drug screens should be used with 2 purposes in mind:
    • Confirm that non-prescribed controlled substances are not present (Rule out abuse)
    • Confirm compliance with prescribed therapy (Rule out diversion)
- Criminal record or court-ordered treatment related to prescription drugs
- Receiving reported drugs from multiple providers without clinical basis
- Concern expressed by patient, family member, law enforcement officer, or other health professional
Other signs of possible abuse or diversion (3741-11-11)

- History of chemical abuse or dependency or illegal drug use
- Appearing impaired or overly sedated during office visit or exam
- Requesting reported drugs by specific name, street name, color, or other identifying marks
- Frequently requesting early refills for reported drugs
- Frequently losing prescriptions for reported drugs
- Sharing reported drugs with another person
- Recurring ER visits to obtain reported drugs
Ohio Automated Rx Reporting System (OARRS)

- “Once the physician has reason to believe that the treatment will be required on a protracted basis”
- Protracted basis is defined in Ohio Administrative Code 4731-11-11 as “a period in excess of 12 continuous weeks”
- “At least once annually thereafter”
Defense and Veterans Pain Rating Scale

- **0**: No pain
- **1**: Hardly notice pain
- **2**: Notice pain, does not interfere with daily activities
- **3**: Sometimes distracts me
- **4**: Can do usual activities
- **5**: Hard to ignore, avoids usual activities
- **6**: Focus of attention, prevents doing daily tasks
- **7**: Hard to do anything
- **8**: Can't bear the pain, unable to do anything
- **9**: As bad as it could be, nothing else

Levels:
- **MILD (Green)**
- **MODERATE (Yellow)**
- **SEVERE (Red)**
How do we Measure Pain?

• Do not use words “happy” or “sad” – scale is intended to measure how one’s pain feels inside, not how their face looks
• Additional questions to consider: How is pain affecting your ability to function?
• Reassess often and adjust care as needed
Acute Pain Management

- Continue scheduled opioids
  - Expect tolerance
  - Be prepared for antagonism of opioid effects with some Medication-Assisted Treatment Regimens

- Scheduled Non-Narcotic Analgesics
  - NSAID’s when appropriate
  - Acetaminophen (oral vs IV)

- Immediate acting narcotic for breakthrough pain (po if possible)

- Regional analgesia
  - Spinal/Epidural techniques
  - Transversus Abdominus Plane (TAP) Blocks
  - Paravertebral blocks/catheters
  - Peripheral nerve blocks/catheters

- Adjuncts
  - Ketamine (Category B)
  - α-2 agonists (e.g. Clonidine, Dexmedetomidine) (Category C)
# Opioid Receptor Subtypes

<table>
<thead>
<tr>
<th></th>
<th>µ</th>
<th>δ</th>
<th>κ</th>
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</thead>
<tbody>
<tr>
<td>Agonist Prototype</td>
<td>Morphine</td>
<td>Deltorphin</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>CNS effects</td>
<td>euphoria</td>
<td>--</td>
<td>dysphoria</td>
</tr>
<tr>
<td>Supraspinal analgesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spinal analgesia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>+</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Sedation</td>
<td>+</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>+</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>+</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Dopamine release</td>
<td>+</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Acetylcholine release</td>
<td>+</td>
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</tbody>
</table>
Heroin

- Rapidly hydrolized to 6-monoacetylmorphine (6-MAM)
- 6-MAM is subsequently hydrolyzed to morphine
- Both heroin and 6-MAM are more lipid soluble and therefore enter the brain more rapidly than morphine
## Medication-Assisted Treatment Regimens

<table>
<thead>
<tr>
<th>Name</th>
<th>Components</th>
<th>Mechanism</th>
<th>$t_{1/2}$</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Methadone</td>
<td>Pure agonist</td>
<td>8 – 59 hrs</td>
<td>Daily po*</td>
</tr>
<tr>
<td>Subutex®</td>
<td>Buprenorphine</td>
<td>Partial agonist</td>
<td>20 - 44 hrs</td>
<td>8-16 mg SL qd</td>
</tr>
<tr>
<td>Suboxone®</td>
<td>Buprenorphine/Naltrexone</td>
<td>Partial agonist/Pure antagonist</td>
<td>20 - 44 hrs</td>
<td>4-24 mg SL qd</td>
</tr>
<tr>
<td>Vivitrol®</td>
<td>Naltrexone</td>
<td>Pure antagonist</td>
<td>5 – 10 days</td>
<td>380 mg IM q4WEEKS**</td>
</tr>
</tbody>
</table>

* Requires daily, monitored administration

** Must be opioid-free $\geq$ 7-10 days to avoid acute withdrawal
# Effects on Opioid Receptor Subtypes

<table>
<thead>
<tr>
<th>Drug</th>
<th>μ</th>
<th>δ</th>
<th>κ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Suboxone®, Subutex®)</td>
<td>+/-</td>
<td>-</td>
<td>--</td>
</tr>
<tr>
<td>Butorphanol (Stadol®)</td>
<td>+/-</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Methadone</td>
<td>+++</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Naloxone</td>
<td>---</td>
<td>-</td>
<td>--</td>
</tr>
<tr>
<td>Naltrexone (Vivitrol®)</td>
<td>---</td>
<td>-</td>
<td>---</td>
</tr>
</tbody>
</table>

A graph showing the relationship between log dose and opioid effect. The graph compares full agonists (Methadone), partial agonists (Buprenorphine), and antagonists (Naloxone).
Acute Pain Management

- Continue scheduled opioids
  - Expect tolerance
  - Be prepared for antagonism of opioid effects with some Medication-Assisted Treatment Regimens

- Scheduled Non-Narcotic Analgesics
  - NSAID’s when appropriate
  - Acetaminophen (oral vs IV)

- Immediate acting narcotic for breakthrough pain (po if possible)

- Regional analgesia
  - Spinal/Epidural techniques
  - Transversus Abdominus Plane (TAP) Blocks
  - Paravertebral blocks/catheters
  - Peripheral nerve blocks/catheters

- Adjuncts
  - Ketamine (Category B)
  - α-2 agonists (e.g. Clonidine, Dexmedetomidine) (Category C)
Ofirmev®

- Pregnancy Category C
- Studies have shown approximate equianalgesic potency to Morphine 10 mg IV
- 1000 mg IV q6h
- Cadence Pharmaceuticals purchased by Mallinckrodt Medical in February 2014 for $1.3 Billion
  - In May 2014, Mallinckrodt announced increase in price from $10 per dose to $34 per dose
Common Oral Narcotics

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Narcotic</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percocet</td>
<td>Oxycodone 5 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td>Vicodin</td>
<td>Hydrocodone 5 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Lortab</td>
<td>Hydrocodone 5 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Tylenol #3</td>
<td>Codeine 30 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Tylox</td>
<td>Oxycodone 5 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

January 2011: FDA issued guidance requesting that manufacturers limit acetaminophen to ≤ 325 mg per pill
## Equianalgesic Oral Narcotics

<table>
<thead>
<tr>
<th>Oral equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine 15 mg po</td>
</tr>
<tr>
<td>Oxycodone 10 mg po</td>
</tr>
<tr>
<td>Hydrocodone 15 mg po (not available as stand alone)</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid) 3.75 mg po</td>
</tr>
<tr>
<td>Tapentadol (Nucynta) 100 mg po</td>
</tr>
<tr>
<td>Codeine 90 mg po</td>
</tr>
<tr>
<td>Tramadol (Ultram) 30 mg po</td>
</tr>
</tbody>
</table>
Codeine

- Actually, a prodrug
- Metabolism mediated by hepatic microsomal CYP2D6 via O-demethylation to its active compound, Morphine
- Patients with mutations in CYP2D6 do not convert Codeine to Morphine and therefore experience reduced or no pain relief
  - 5-10% of Caucasian population
- In contrast, rapid metabolizers are susceptible to increased effects from Codeine administration, because rapid metabolism results in a higher systemic concentration of Morphine
  - 1-7% of Caucasian population
  - Rapid metabolizers may experience more benefit
  - Rapid metabolizers may be more prone to misuse/abuse
Oral Narcotic Metabolites

- Hydrocodone is also metabolized via the CYP2D6 system

- Drugs that undergo pure glucuronidation (Morphine, Hydromorphone) may be less prone to drug-drug interactions and genetic variability in response
  - Morphine is metabolized to Morphine-6-glucuronide, which is an active metabolite
Common Pain Syndromes in Pregnant Patients

Chronic
- Low back pain
- Migraine headaches

Acute
- Nephrolithiasis
- Orthopedic fractures
- Non-obstetric surgery
- Post-C/S pain management
Low Back Pain

- Outcomes for acute low back pain without new neurologic deficit are the same regardless of imaging or therapeutic approach for the first 30 days.

- Consider imaging and referral to pain medicine or spine specialist when:
  - Immediately if there is a new neurologic deficit
  - Symptoms persist > 30 days

- Encourage light activity (not bedrest) and use of NSAID’s for symptomatic relief
  - Substitute Acetaminophen for NSAID’s during 3rd trimester due to concerns re: premature ductal closure
Non-Narcotic Treatment of Low Back Pain

- NSAID’s (or acetaminophen if NSAID’s are contraindicated)
- Physical Therapy
- Chiropractic
- Ice (or ice alternating with heat)
- Massage
- Proper shoes

Interventional Pain Management
- Interlaminar ESI’s can be performed without fluoroscopic guidance in pregnant patients
- Trigger Point Injections
- SI Joint injections and Medial Branch Blocks can theoretically be performed with Ultrasound guidance

Cyclobenzaprine (Flexeril)
- Category B
- Sedative effects
  - Can be useful in those seeking sedative/hypnotic effects of benzodiazepines and/or opiates
  - Particularly useful before bedtime
Common Pain Syndromes in Pregnant Patients

Chronic
- Low back pain
- Migraine headaches

Acute
- Nephrolithiasis
- Orthopedic fractures
- Non-obstetric surgery
- Post-C/S pain management
Management of Post-C/S Pain in the Opioid-Dependent Parturient

- Neuraxial Duramorph
- Continue long-acting maintenance narcotics
- Scheduled NSAID’s
- Scheduled Acetaminophen (oral vs intravenous)
- Immediate-acting oral narcotic prn for breakthrough pain
- Consider “heroic” measures for refractory/difficult cases:
  - Low-dose Ketamine
  - Transversus Abdominus Plane Blocks/Catheters
# Ofirmev for Post-C/S Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Inal (2007) (N = 50)       | • Ofirmev 1000 mg IV X 1  
                          • Meperidine 100 mg IV X 1                                               | • Mean VAS lower at all time points (0-120 minutes)  
                          • Average time to 1st rescue 6 hrs in Ofirmev vs 2 hours in Meperidine |
| Kiliclasan (2010) (N = 50) | • Ofirmev 1000 mg IV q6h X 48 h  
                          • Placebo IV q6h X 48h                                                     | • VAS lower in Ofirmev group at all time points (0-24 hrs) (p<0.05)  
                          • Cumulative rescue analgesia (Tramadol) lower in Ofirmev group (P<0.05) |
| Mitra (2012) (N = 204)     | • Ofirmev 1000 mg IV q6h X 24h  
                          • Tramadol 75 mg IV q6h X 24h                                               | • Less nausea in Ofirmev group (2.0% vs 14.6%, p=0.001)  
                          • No difference in pain intensity  
                          • No difference in rescue analgesics                                       |
| Omar (2011) (N = 80)       | • Ofirmev 1000 mg IV q6h X 24h  
                          • Placebo IV q6h X 24h                                                      | • Lower median VAS at 6, 12, & 24 hours in Ofirmev group (p< 0.05)  
                          • Decreased use of rescue medication (0% vs 20%, p<0.05)                 |
| Alhashemi (2006) (N = 45)  | • Ofirmev 1000 mg IV + Placebo PO q6h X 48h  
                          • Ibuprofen 400 mg po q6h + Placebo IV q6h X 48h                       | • No difference in VAS or rescue  
                          • More N/V in Ofirmev group (p=0.05)  
                          • More pruritus in Ibuprofen group (p=0.031)                            |
Management of Post-C/S Pain in the Opioid-Dependent Parturient

- Neuraxial Duramorph
- Continue long-acting maintenance narcotics
- Scheduled NSAID’s
- Scheduled Acetaminophen
- Immediate-acting oral narcotic prn for breakthrough pain
- Consider “heroic” measures for refractory/difficult cases:
  - Transversus Abdominus Plane (TAP) Blocks/Catheters
  - Low-dose Ketamine
Transversus Abdominus Plane (TAP) Block

- Described by Rafi in 2001
- Anterior rami of thoracolumbar nerves that innervate anterior abdominal wall and parietal peritoneum pass through this plane
- Provides anesthesia of abdominal wall from T10-L1
Pregnancy is associated with increased sensitivity to local anesthetic effects.

Caution in patients who have been receiving local anesthetic via labor epidural analgesia.

TAP Block is a field block, requiring large volume of local anesthetic:
- ≥ 25 ml of long acting local anesthetic (e.g. Bupivacaine 0.25%) per side.

Can also place catheters for postoperative infusion X 48 hrs.

- 5 trials
- 312 patients
- Excluded spinal morphine

Results
- TAP block reduced 24 hour IV rescue Morphine consumption by 24 mg
- TAP block decreased VAS pain score by 0.8 cm
- TAP block decreased the incidence of opioid side effects
- No improvement when spinal morphine was administered

- 9 trials

**Results**

- Decreased opioid consumption at 6, 12, and 24 hours
- Decreased pain scores for up to 12 hours in patients not receiving intrathecal morphine
- Compared to intrathecal morphine, TAP block led to:
  - Longer interval to 1st rescue analgesic
  - Decreased opioid consumption
  - Small decreased in pain score with movement
Management of Post-C/S Pain in the Opioid-Dependent Parturient

- Neuraxial Duramorph®
- Continue long-acting maintenance narcotics
- Scheduled NSAID’s
- Scheduled Acetaminophen
- Immediate-acting oral narcotic prn for breakthrough pain
- Social Services consult while inpatient
- Consider “heroic” measures for refractory/difficult cases:
  - Transversus Abdominus Plane (TAP) Blocks/Catheters
  - Low Dose Ketamine
Ketamine

- NMDA receptor antagonist
- Phencyclidine (“PCP”) derivative
- “Dissociative anesthesia”
- Unique among IV anesthetics in producing significant analgesia
- Use as agent for induction or maintenance of general anesthesia limited by unpleasant psychomimetic side effects
Ketamine Side Effects

- Excessive Salivation & Lacrimation
- Nystagmus, diplopia
- Psychotropic effects
- Increases HR, BP, and CO (via central stimulation of Sympathetic Nervous System)
- Increases CMRO2 and CBF
- Relaxes bronchial smooth muscle
- Maintains CO2 responsiveness
Low Dose Ketamine

- NMDA receptor antagonism may reduce excitatory neurotransmission that leads to opioid-induced hyperalgesia

- Ketamine 0.2-0.8 mg/kg IV or IM bolus useful during regional anesthesia (e.g. during C/S)

- Ketamine 0.05-0.1 mg/kg/hr IV gtt X 24-48 hrs post-op
Low Dose Ketamine Infusion

1. While on Ketamine infusion, follow anesthesia orders. Ondansetron (Zofran) and acetaminophen may be administered if ordered by the surgeon. All other medications or sedatives need approval by anesthesia.

2. Communication to receiving unit must be completed prior to the initiation of Ketamine infusion.

3. Apply monitoring devices.

4. Vital signs and sedation level every hour times 6 hours, then every 2 hours until any change in condition, while on intravenous Ketamine infusion (see Ketamine Flow Sheet).

5. Continuous 0% oxygen monitoring. Saturate oxygen to keep at 90% at 92%.

6. Monitor/induced patient to report the following symptoms:
   - Confusion, hallucinations, delirium, fear, paranoia, panic reaction
   - Visual disturbances (e.g., shaking, diplopia, blurred vision)
   - Enhanced skeletal muscle tone
   - Nausea, vomiting
   - Excessive salivation

   Monitor for and report to anesthesia any symptoms described above by the patient and:
   - Respiratory rate less than 10
   - Heart rate less than 60 or greater than 110
   - Oxygen saturation less than 92%
   - Skewed muscle hyperactivity
   - Inadequate pain relief
   - Cuff for systolic blood pressure less than 90 or greater than 180

7. Use a dedicated infusion line of 0.9% saline solution at 25 mL per hour. Connect Ketamine infusion to dedicated IV port for infusion.

8. Maintain IV access. 12 hours after discontinuation of intravenous Ketamine infusion.

9. Available only with assistance.

10. Bedside medication charting at all times.

11. Do not adjust Ketamine dose without authorization from anesthesia.

12. Cuff anesthesia if sedation scale greater than or equal to 4 (predominant, difficult to arouse or minimal response to stimulation)

13. Notify surgeon when Ketamine infusion is discontinued for further pain medication.

Additional Medication Orders—Write in or check the boxes to activate the orders.

14. Ketamine: 120 mg/mL 0.9% saline solution at ____ mg per hour
    (Anesthesiologist: recommended starting dose range 1-7.5 mg/hour)

   Lidocaine or Ketamine IV infusion dose: 25 mg/hour

   Physician's Signature Date: Time: Physician's Handwritten Signature/Initial(s) and Initial(Initial(s))
Summary

- Unintentional Rx drug overdose has reached epidemic proportions
- Narcotics have limited utility in the management of chronic non-malignant pain
- Continue long-acting maintenance agents during acute pain episodes
  - Consider holding morning dose of Suboxone® AM of surgery
- Maximize non-narcotic analgesics (NSAID’s, Acetaminophen) & regional anesthesia techniques
- Reserve narcotics for acute breakthrough pain