Disclosures

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

• Review the recent federal regulations related to opioid analgesic prescribing.
• Develop guidelines for the use of ketamine as an analgesic and/or sedative agent for burn patients.
• Describe the role of gabapentinoids in multimodal analgesia for burn patients.

Regulatory Changes & Challenges:
Targeting Abusers not Appropriate Users

Clinical Case #1

• MB is 25yof was discharged from the burn service 1 week ago with on-going dressing changes to her chest/abdomen.
• She had a discharge prescription filled at that time.
• Today, she brings in a new prescription for more oxycodone/acetaminophen to her local pharmacy.
• The pharmacist questions the legitimacy of her prescription.

Why would there potentially be issues?

The Challenges

• 2013: ~6.5 million people ages ≥ 12 years used prescription drugs without a legitimate medical reason
• Opioid use: ~718 mg of morphine / person
• 2015: DHHS initiative to reduce prescription opioid- and heroin-related overdose, death and dependence.
• 2016: CDC Guideline for Prescribing Opioids for Chronic Pain – United States
Regulations

- Title 21: Code of Federal Regulations – section 1306.04: “a prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his/her professional practice”
- Controlled Substances Act:
  - Prescription requirements
    - Date on prescription must be the date you write it
    - Write the quantity both in number and words
  - E-prescribing – must have appropriate software & 2 identifiers
  - Know your state requirements

Mid-level Controlled Substance Prescribing

- Each state is different
- Must obtain your own DEA# to prescribe
- DEA Reference:
  https://www.deadiversion.usdoj.gov/drugreg/practioners/

2015 DHHS Initiatives

- Provide training and educational resources, including updated prescriber guidelines
  https://www.hhs.gov/opioids/health-professionals-resources/
- Increase the use of naloxone – development and distribution to decrease opioid / heroin deaths
- Expand the use of Medication-Assisted Treatment for abuse and dependence

How do these initiatives affect you?

- Burn patients have legitimate pain issues –
  - Providing the ICD-10 diagnosis on the outpatient prescription
  - If your institution has a discharge / outpatient pharmacy – get to know the staff
- Burn patients deal with both acute and chronic pain
- Availability of opioid medications
  - Distributors may restrict order size from institutions
  - Institutions then face a potential limited quantity (inpatient and outpatient)

Pain Management in the Burn Patient: A Multimodal Approach
Pain & the Burn Patient

- Background pain due to injury – constant, dull
- Post-operative pain
- Procedural pain during dressing changes, etc.
  - Anxiety-induced pain surges
  - Opioid-induced hyperalgesia
- Neuropathic pain

Goals of Therapy

- Alleviate patient discomfort
- Reduce anxiety associated with procedures
- Allow for appropriate dressing changes / rehabilitation
- Prevent / Minimize:
  - Depression
  - Suicidal ideations
  - Anxiety
  - Post-traumatic stress disorder

Clinical Case #2

- 44yom s/p 49% TBSA burns
- ICU, mechanically ventilated
  - Fentanyl IV-drip at 350 mcg/hr
  - Midazolam IV-drip at 2 mg/hr
  - Oxycodone 20mg per tube Q4H
- Recent medication requirements for dressing changes:
  - Morphine sulfate 60 mg per tube 1 hour prior
  - Fentanyl 500 mcg IVP (total)
  - Midazolam 20 mg IVP (total)

Clinical Case #2

Concerns regarding this patient:

- He’s developing tolerance
- Unable to wean the ventilator

What other analgesic options may work?

The “Ideal” Analgesic

- Rapid onset, short duration for procedures
- Long-acting option
- No CNS depression
- No respiratory depression
- Low tolerance or addictive potential
- Minimal to no side effects

Pharmacotherapy Options

- Opioid analgesics
- Ketamine
- Gabapentin / pregabalin
- Clonidine
- Acetaminophen
- Lidocaine

Retrouvey H. J Burn Care Res. 2015;36:315.
Pharmacotherapy Options

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  - Ketamine
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  - Clonidine
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Opioid Analgesics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>IR PO: 30 min / IV: 5-10 min</td>
<td>3 – 5 hrs</td>
<td>Histamine-release itching may help with PTSD</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>IR PO: 10-15 min</td>
<td>3 – 6 hrs</td>
<td>Less itching vs. morphine</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV: immediate / IV: 30 – 60 min</td>
<td></td>
<td>Procedural analgesia ICU analgesodination</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>1 – 3 min / 3 – 10 min</td>
<td></td>
<td>Ultra-short acting respiratory depression</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Within 1 min / 30 – 60 min</td>
<td></td>
<td>Shorter acting vs fentanyl / Acute severe pain after stopped</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO: 30-60 min</td>
<td>Single dose: 4 - 8 hrs Repeated: 22 - 48 hrs</td>
<td>Mu receptor &amp; NMDA QT prolongation</td>
</tr>
</tbody>
</table>

Pharmacotherapy Options

- Ketamine

Ketamine: An Old Drug Making a Come-back

Opioid-Induced Hyperalgesia

- Risk Factors:
  - Daily dressing changes / debridement
  - Repeated exposure to opioid analgesics
- Presentation:
  - Increased sensitivity / response to pain
  - Increasing opioid analgesic requirements without relief
- Mechanism (theorized):
  - Continuous or repeated stimulation of nociceptive afferent fibers
  - Increased dorsal horn excitability with repeated stimulation
  - Disinhibition of central neurons mediated by NMDA receptors
  - Changes in levels of spinal cytokines & chemokines

Pharmacotherapy Options

- Opioid analgesics
  - Ketamine
  - Gabapentin / pregabalin
  - Clonidine
  - Acetaminophen
  - Lidocaine

Brief History of Ketamine

1962: Synthesized as a derivative of phencyclidine (PCP)
1960-70s: mostly anesthesia, recreation use
1980s: Use in burn patients

Present: Increased interest as ICU sedative, analgesic

Pharmacotherapy Options

- Opioid analgesics
  - Ketamine
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Brief History of Ketamine

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1980s: Use in burn patients

Present: Increased interest as ICU sedative, analgesic
Mechanism(s) of Action: Analgesia

- Non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist
- Ketamine attenuates the development of central sensitization, opioid tolerance, and opioid-induced hyperalgesia
  - Decrease in acute pain
  - Potential for preventing chronic pain
- Analgesic effects occur at sub-anesthetic doses (≤ 0.3 mg/kg IV)

Pharmacokinetics

- Onset:
  - IV: 30-40 seconds
  - IM: 1-2 minutes
  - Oral: 30 minutes
- Analgesic duration: 5-60 minutes
- Highly lipid soluble
- Metabolism: metabolite 33% activity of parent
- Elimination half-life = 2-3 hours

Adverse Effects of Ketamine

- Psychomimetic effects
- Sedation
- Increase in blood pressure
- Increase in heart rate, cardiac index
- Increase in oral secretions
- Increase in intraocular pressure
- Nystagmus, diplopia

Role in Burn Patients

- ICU analgesia or sedation
- Procedural analgesic and amnestic
- Prevention of post-traumatic stress disorder?

- QUESTIONS:
  - Dosing: Bolus vs. Continuous Infusion
  - IV versus Oral
  - Monotherapy or Combination

Ketamine IV/IM Dosing

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Pharmacokinetics</th>
<th>Place in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular (IM): 2-4 mg/kg IM</td>
<td>Onset 1-4 minutes Duration 15-30 minutes</td>
<td>Outpatient therapy</td>
</tr>
<tr>
<td>IV Bolus: 0.5-1 mg/kg IV (0.5 mg/kg q5min prn)</td>
<td>Onset 30-40 seconds Duration 5-10 minutes</td>
<td>Short procedures</td>
</tr>
<tr>
<td>IV Continuous Infusion 0.5-1 mg/kg bolus, then 0.05-0.5 mg/kg/h ~ pain 0.5-5 mg/kg/h ~ sedation</td>
<td>Onset: 30-40 seconds Rapidly titratable</td>
<td>ICU analgesia ICU sedation (high dose) Long procedures Opioid tolerant patients</td>
</tr>
</tbody>
</table>

*Ketamine in the Burn Population

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces opioid use by 30%</td>
<td>Potential sympathetic activation</td>
</tr>
<tr>
<td>Preserves cardiovascular stability</td>
<td>(↑ HR, ↑ BP)</td>
</tr>
<tr>
<td>Promotes gut motility</td>
<td>Laryngospasm (0.4%)</td>
</tr>
<tr>
<td>Maintains spontaneous breathing</td>
<td>Psychomimetic effects (12-50%)</td>
</tr>
<tr>
<td>Rapid onset, short duration</td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate, BP = blood pressure

*Pretreat with low-dose benzodiazepine to mitigate psychomimetic effects
Ketamine Dosing

- Choose the route based on access & desired duration
  - IV: rapid onset, short duration
  - IV Infusion: rapid onset, long duration
  - IM: long duration, no IV access
- Consider adding continuous infusion ketamine for ICU analgesedation in patients requiring high-dose opioids

Combination Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacPherson RD. (2006) Prospective Observational</td>
<td>n=49</td>
<td>PCA: Tnl/kg dose Ketamine 10mcg Midazolam 0.5mcg</td>
<td>Mean dose Ketamine 1-0mg Midazolam 4.5mcg Flattened effective 0.5/10 times</td>
<td>90min procedures 25% hallucinations 11% desaturation (SaO2 &lt; 95%)</td>
</tr>
<tr>
<td>Zor F. (2010) 20-50% TBSA Prospective, RCT (Turkey)</td>
<td>n=24</td>
<td>1. Ketamine 2mcg/kg IM 2. Tranquil 1mg/kg IM 3. Ketamine 2mcg/kg IM 4. Midazolam 0.5mg/kg IM 5. Ketamine 2mg/kg</td>
<td>Ketamine only higher HR higher SBP Combinations significantly lower pain scores vs ketamine only</td>
<td>RM route Excluded intubated patients 40min procedures</td>
</tr>
<tr>
<td>Gündüz M. (2011) 10-25% TBSA Prospective, RCT</td>
<td>n=90</td>
<td>1. Dexmedetomidine IM Ketamine 1mg/kg IV 2. Midazolam 0.5mg/kg IV Ketamine 1mg/kg IV 3. Ketamine 1mg/kg IV</td>
<td>No difference in pain scores</td>
<td>Group 1: Longer sedation/lower SBP Well tolerated</td>
</tr>
</tbody>
</table>

Oral vs. IV Ketamine

- Oral Ketamine
  - 20-30% bioavailability
  - Onset ~30 minutes
  - Duration ~60 minutes
- Oral ketamine compounded using injectable

Oral Ketamine for Dressing Changes

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norambouza C (2013) ≤ 10% TBSA Prospective, RCT Pediatric: 1-5 y</td>
<td>n=80</td>
<td>1. Midazolam 0.5mcg/kg PO Ketamine 5mcg/kg PO Midazolam 0.5mcg/kg PO Acetaminophen 10mg/kg PO Codeine 1mg/kg PO 20min before dressing change</td>
<td>Lower pain scores with ketamine No difference in sedation More ADE with ketamine: primarily nystagmus First dressing change only</td>
<td></td>
</tr>
<tr>
<td>Kundra P (2015) 20-50% TBSA Prospective, RCT Crossover Adults</td>
<td>n=80</td>
<td>1. Ketamine 5mcg/kg PO 2. Desmedetomidine 4mcg/kg PO Concurrent: Morphine 0.1mg/kg IM q6h Diazepam 5mg PO q12h Topical bupivicaine</td>
<td>Ketamine higher sedation scores Decreased pain but larger &amp; sustained decrease with ketamine More delirium with ketamine Excluded: facial burns, electrical burns, psychiatric disorders, Diabetes, Hypertension No HR change MAP lower w/ desmedetomidine</td>
<td></td>
</tr>
</tbody>
</table>

Ketamine to Prevent PTSD

- All retrospective data
- Combat injuries and burn injuries
- McGhee LL (2008) – lower prevalence of PTSD among patients treated with ketamine (27% vs 46%)
- McGhee LL (2014) – no difference
- Mion G (2017) – ketamine not a risk factor for PTSD
Ketamine Therapy - Summary

- Route of administration will alter onset & duration
- Continuous infusion – both ICU & procedural analgesia
- Combination therapy (with another sedative):
  - Decreased pain scores during dressing changes
  - Decreased adverse events (hallucinations)
  - May prolong sedation
- Oral may be an option
- Caution in patients with history of psychiatric disorders or glaucoma

Pharmacotherapy Options

- Opioid analgesics
- Ketamine
  - **Gabapentin / pregabalin**
- Clonidine
- Acetaminophen
- Lidocaine

Gabapentinoids:

*Do they make a difference?*

**Gabapentin**

- Decreases central sensitization and indirectly inhibits NMDA receptor over activation
- Dosing: 100-1200 mg PO TID (max 3600mg/day)
- Renal adjustment
- Maximal effect may take 2 months
- Common Adverse Events:
  - Dizziness (17-28%)
  - Somnolence (19-21%)
  - Mood changes in children (4-8%)

- Newer structural analog of gabapentin
- Clinical efficacy in reducing peripheral and central neuropathic pain, anxiety, and improving sleep
- Analgesic effect within 1 week

**Table: Gabapentin**

<table>
<thead>
<tr>
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<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimaz S. (2012)</td>
<td>50</td>
<td>Gabapentin 1200 mg 2 hr prior to surgery 1. Placebo 2. Post-op morphine PCA</td>
<td>Gabapentin patients:</td>
<td>Multiple exclusions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morphine requirements 1. Pain scores 2. Similar sedation 3. No difference in N/V</td>
<td></td>
</tr>
<tr>
<td>Cugnet O. (2007)</td>
<td>20</td>
<td>Gabapentin 800mg PO TID x 21 daysStart day 3 2. Historical control Concurrent: Morphine, tramadol, paracetamol</td>
<td>Gabapentin patients:</td>
<td>No difference in itching 30% somnolence in gabapentin patients No mention of renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Morphine requirements 1. Pain scores 2. Results consistent throughout patient stay</td>
<td></td>
</tr>
<tr>
<td>Wibbenmeyer L. (2014)</td>
<td>53</td>
<td>Gabapentin 300mg PO TID up to 1200mg PO TID 2. Placebo</td>
<td>No difference:</td>
<td>Excluded renal insufficiency 5-20% TBSA burns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain scores 1. Neuropathic pain 2. Opioid consumption</td>
<td></td>
</tr>
</tbody>
</table>

Pregabalin

- Newer structural analog of gabapentin
- Clinical efficacy in reducing peripheral and central neuropathic pain, anxiety, and improving sleep
- Analgesic effect within 1 week
### Pregabalin

<table>
<thead>
<tr>
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<th>n</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong L. (2010)</td>
<td>13</td>
<td>Pregabalin 75mg PO BID up to 300mg PO BID max</td>
<td>89% reduction in pain scores</td>
<td>Recruited 24, 11 lost to follow-up 5/13 stopped for personal reasons</td>
</tr>
<tr>
<td>≥ 5% TBSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Retrospective Outpatient clinic c/o neuropathic pain
- n=13
- Planned dose titrated based on reported symptoms

- Wong L. (2010): 5-40% TBSA
- Prospective RCT 1st 28 days after burn
- n=90
- Excluded if history of neuropathic pain
- Stratified by %TBSA

### Gabapentin vs Pregabalin

<table>
<thead>
<tr>
<th>Gabapentin</th>
<th>Pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 3 times per day dosing</td>
<td>• 2 times per day</td>
</tr>
<tr>
<td>• Slow titration</td>
<td>• Rapid titration</td>
</tr>
<tr>
<td>• Maximal effect 2 months</td>
<td>• Pain relief at ~1 week</td>
</tr>
<tr>
<td>• Burn patients</td>
<td>• Burn patients:</td>
</tr>
<tr>
<td>• Improved perioperative analgesia</td>
<td>• Improved pain scores</td>
</tr>
<tr>
<td>• ± decrease opioid doses</td>
<td>• No change in opioid doses</td>
</tr>
</tbody>
</table>

- Similar adverse events
- Both require renal adjustment

### Pharmacotherapy Options

- **Opioid analgesics**
- **Ketamine**
- **Gabapentin / pregabalin**
- **Clonidine**
- **Acetaminophen**
- **Lidocaine**

### Summary

- **DHHS initiatives impact all of us – stay alert to changes**
- **Opioids are a mainstay – but don’t forget alternatives**
- **Ketamine:**
  - Opioid sparing
  - Procedural analgesic in non-intubated / intubated patients
  - Multiple routes
  - ICU analgesedation
- **Gabapentin probably has a pre-operative role**
- **Efficacy of gabapentin / pregabalin for routine therapy may help select patients but doesn’t decrease opioid analgesic requirements**

### Pain Management Pearls

Kara L. Birrer, Pharm.D., BCPS
Clinical Pharmacist, Surgical / Neurocritical Care

March 21, 2017