END OF LIFE CARE: PAIN MANAGEMENT

W. David Clark, MD
Disclaimer

I have no financial interests or relationships with any manufacturers of products or providers of services I may reference in my presentation.
Objectives

• Discuss pain in the larger context of suffering
• Identify the differences between nociceptive and neuropathic pain
• Review pharmacological treatment strategies for nociceptive and neuropathic pain
• Discuss management of rapidly escalating pain
Chronic non-cancer pain is a separate entity from EOL pain, with different management principles and challenges.
Fast Facts and Concepts

www.capc.org

“For Providers”
Care Settings

• Office
• Care Center/Nursing Home
• Hospital
• Hospice Room in Community Hospital
• Home
3 C’s of Symptom Management

• Comfortable
• Contented
• Connected
Pain Management in Family Medicine

- Know the story
- Match pharmacology to individual need
- Titrate medication to response
- Communicate effectively
- Understand OME
- Understand opiate incomplete cross-tolerance
- Be able to recognize and reverse opiate toxicity
- Be able to manage a pain crisis
Pain Definition

“…….a somatic perception containing: (1) a bodily sensation with qualities like those reported during tissue-damaging stimulation, (2) an experienced threat associated with this sensation, and (3) a feeling of unpleasantness or other negative emotion based on this experienced threat.“

Total Pain

- Physical
- Emotional
- Social/relational
- Spiritual
- Bureaucratic
Physical

Mental

Spiritual

Acknowledgement
Spiritual
Mental
Physical
“Death is not a strictly medical event, and many patients’ and families’ most pressing needs are not medical in nature.”

Panel comments, *Dying in America: Improving Quality and Honoring Individual preferences Near the End of Life*, Institute of Medicine. [http://www.iom.edu/Reports](http://www.iom.edu/Reports). Released 9/14/14
“The patient’s story is the container for meaning.”

Rachel Naomi Remen
End of Life

• No exact definition
• Multiple trajectories to death
• NIH
  “People can, in some respects, be considered to be approaching death from the moment they are born.”
  National Institutes of Health. National institutes of health state-of-the-science conference statement of improving end-of-life care,

• Practical working definition: life-limiting illness with high likelihood for death within 6-12 months
Pain

- Location
- Quality
- Quantity
- Setting
- Chronology
- Associated symptoms
- Aggravating and alleviating factors
Intensity

- Awareness 1-2
- Nuisance 3-4
- Aggravation 5-6
- Preoccupying ("All I think about") 7-8
- Excruciating ("Worst ever") 9-10
Wong-Baker Facial Pain Scale

0  NO HURT
1  HURTS LITTLE BIT
2  HURTS LITTLE MORE
3  HURTS EVEN MORE
4  HURTS WHOLE LOT
5  HURTS WORST
No Pain

Worst Pain Ever
Nociceptive Pain

A **nociceptor** is a nerve fiber preferentially sensitive to a noxious stimulus.

**Nociceptive pain** is the perception of nociceptive input, usually due to tissue damage.

Rosenquist E, Aronson M, Park L. *Definition and pathogenesis of chronic pain*. UpToDate
Nociceptive Pain

• Somatic
  • Arises from injury to body tissues
  • Well localized but varies in description and experience

• Visceral
  • Arises from viscera mediated by stretch receptors
  • Poorly localized
  • Deep, dull, cramping

Rosenquist E, Aronson M, Park L  Definition and pathogenesis of chronic pain. UpToDate
Neuropathic Pain

- Pain caused by a primary nerve injury or dysfunction in the nervous system
- Responsible lesion may be of any type and occur at any location along the sensory transmission pathways
- May be directly related to a life-threatening disease or by a co-morbidity
- May be constant or fluctuating intensity
- May be paroxysmal
- May be spontaneous or provoked by stimulus
- Descriptors may help identify pain as neuropathic

Neuropathic Pain Descriptors

- Burning
- Sharp
- Stabbing
- Squeezing
- Shooting
- Pins and needles
- Electric shock
- Cold
Patients often have combination of neuropathic and nociceptive pain ("mixed pain"). Effective pain management should address both types.
Start Simple

- Acetaminophen (Scheduled)
  - Caution
    - Liver disease
    - Pts on warfarin
  - Avoid alcohol with significant scheduled doses
  - Avoid single agent + combination analgesic products

- NSAIDS
  - Caution:
    - Renal disease
    - Hypertension
    - History of ulcers/GI bleeding
    - CHF
    - Advanced liver disease
    - Concurrent anticoagulants
Codeine

- Constipating
- Direct anti-tussive effect
- Metabolic Variation
  - Converted to MORPHINE via CYP2D6 pathway
  - Approximately 7% of Caucasians lack CYP2D6 activity
    - Negligible analgesic effect in these patients
  - “Ultra-rapid metabolizers” (small subset)
    - Potential for extensive conversion to morphine and associated adverse effects
    - Impact may be greatest in pediatric population
Tramadol

- Weak opioid mu-receptor agonist
- Inhibits uptake of serotonin and norepinephrine
  - SNRIs have the same effect
- Fairly rapid pain relief
- Potential to ↓ seizure threshold
- Serotonin syndrome potential
  - SNRI
  - SSRI
- Start with 50 mg PO every 4 hours
- Maximum dose 400 mg/day
- Renal or hepatic impairment requires dose adjustment

Hydrocodone

- Hydrocodone + acetaminophen
  - Vicodin
  - Lortab
- In 2007, 99% of worldwide hydrocodone consumed in US
  
  International Narcotics Control Board Report 2008
- Schedule III → Schedule II August 2014
- Converted via CYP2D6 pathway to HYDROMORPHONE
- Zohydro ER approved by FDA in 2014
  - Concerns re: potential for substance abuse
  - FDA review panel recommended 12-2 against approval
  - 30 US states requested that it not be approved in capsule form

Rita Rubin
WebMD Health News
2/27/14
# Opioid Equivalents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral/Rectal (mg)</th>
<th>IV/SC (mg)</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>N/A</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>N/A</td>
<td>100 mcg (single dose)</td>
</tr>
</tbody>
</table>
Opiate Adverse Reactions

- **Constipation**
  - All patients on regular opiates must have a bowel regimen prescribed
    - Docusate has no proven efficacy
    - Stimulant (sennoside) excellent first choice

- **Sedation**
- **Pruritus**
- **Urinary Retention**
- **Nausea**
- **Neuro-excitability**
  - Myoclonus
  - Allodynia
    - Ordinarily non-painful stimuli evoke pain
Opiate Principles

- Respiratory depression risk highest in opioid-naïve pts
- Start low and titrate
- Prescribe smaller amounts of short-acting opiate initially
- See patients 1-2 times/wk to adjust dosages until pain is consistently in 2-3/10 range
- Avoid mixing opiates when possible
  - Morphine SR BID + oxycodone Q 4 hours PRN
- One SR opiate (when appropriate) + one IR
- Goal is pain controlled to patient’s satisfaction
Initial Opioid Dosing

- **Morphine**
  - 2.5-5 mg PO q. 2-4 hours PRN
  - 1 mg IV/SC q. hourly PRN

- **Hydromorphone**
  - 1 mg PO q. 2-4 hours PRN
  - 0.1-0.2 mg IV/SC q. 1 hour PRN

- **Fentanyl**
  - 12-25 mcg IV/SC q. 1 hour PRN

- **Hydrocodone/Acetaminophen**
  - 2.5-5 mg PO of the hydrocodone component
  - Hepatic CYP2D6 $\rightarrow$ hydromorphone
# Opiates in Renal or Hepatic Dysfunction

## Renal
- **Codeine**
  - Do not use
- **Fentanyl**
  - Generally safe
  - May need dose reduction
- **Hydromorphone**
  - 3-glucuronide metabolite can accumulate
- **Methadone**
  - Safe
- **Morphine**
  - Use with caution
  - Active metabolites can accumulate
- **Oxycodone**
  - Caution
  - Parent drug and metabolites can accumulate

## Hepatic
- **Codeine**
  - Do not use
- **Fentanyl**
  - Generally safe
  - No dose adjustment necessary (1 dose)
- **Hydromorphone**
  - Caution
  - Reduce dose by 50%
- **Methadone**
  - Do not use long-term
  - May accum in severe hepatic dysfunction
- **Morphine**
  - Use with caution
  - Conversion to inactive metabts may not happen; increase dosing intervals
- **Oxycodone**
  - Use with caution
  - Reduce initial dose 50% and monitor

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Methadone

- Racemic mixture of d- and l-isomers
  - d-isomer is not an opiate but a potent N-methyl-D-aspartate antagonist
    - Analgesia in neuropathic pain
- Long plasma half-life (can range from 12 to 150 hours)
- Steady state may take up to 4 weeks to achieve
- Doses should not be changed more frequently than weekly unless the patient is in a closely monitored setting
- Potential for QTc prolongation
  - Watch drug interactions
  - EKG in selected patients
  - Caution in doses > 100 mg per day
- **Should only be used by clinicians familiar with its unique properties**

Brglio K, Abrahm J, Savarese D. Pain assessment and management in the last weeks of life. UpToDate
Opiate Stewardship Education

• Sharing opioid medication with others may cause them to have serious reactions or death
• Selling or giving away opioid medication is illegal
• Store in safe AND secure place
  • Children
  • Family members
  • Household visitors
    • Wanted and unwanted
  • Pets
• Proper disposal of unused medication
  • Used fentanyl patch still has enough medication to harm or kill a child

Behaviors Suggestive of Misuse

- Adverse life consequences (e.g., a lost job, relationship problems)
- Current abuse of other substances
- Indications of drug seeking behavior (e.g., seeks early refills)
- Lack of cooperation with opioid treatment plan (e.g., does not follow up with clinical team, refuses to use nonopioid therapies)
- Lack of reliability taking drug (e.g., self-titrates drug, runs out early)
- Loss of control of drug use (e.g., loses prescriptions)

Treatment Options for Neuropathic Pain

• First Line Pharmacologic Choices
  • Tricyclic antidepressants
  • Topical lidocaine
  • Gabapentenoids
    • Gabapentin
    • Pregabalin
  • Selective serotonin noradrenergic reuptake inhibitors (SNRIs)
    • Venlafaxine
    • Duloxetine

Tricyclic Antidepressants

• Extensive literature re: efficacy
  • Efficacy questionable in HIV and chemo Rx associated neuropathy
• Inexpensive
• Anti-cholinergic adverse effects may be limiting factor
  • Secondary amine TCA better tolerated (nortriptyline; desimpramine)
• Start with 10 mg @ HS
• Increase by 10-25 mg every 3-7 days → 75-100 mg
• Avoid or use with caution in elderly
• Avoid or use with great caution in pts with cardiac conduction disturbances or arrhythmia
• Contraindicated after recent MI
• Discuss with pharmacology consultant if any questions
SNRI’s

• Duloxetine
  • Efficacy best shown in diabetic neuropathy
    • Evidence for efficacy in chemotherapy induced neuropathy
  • Adequate trial is 4 weeks
  • Nausea is most common adverse effect
  • Start 30 mg daily for 1 week, then increase to 60 mg daily
  • No significant BP or cardiovascular effects

• Venlafaxine
  • Two to for weeks needed to titrate to effective dose (150-225 mg/day)
  • Adequate trial is 4-6 weeks
  • Potential to increase BP
  • Must taper if treatment discontinued
    • Potential for very uncomfortable withdrawal syndrome

Topical Lidocaine

- Efficacy of 5% lidocaine patch established in RCTs studying different types of NP pain
- Main use is for localized NP
- Helpful for allodynia
- Mild local reactions are main adverse reaction
- No significant systemic reactions or drug interactions
- Lidocaine 5% gel less expensive than patch and has demonstrated efficacy

**Gabapentin**

- Binds to voltage-gated calcium channels and inhibits neurotransmitter release
- Dose dependent dizziness and sedation
- Start at low doses (100 mg @ HS for elderly; otherwise 100 mg TID) and titrate gradually
- Dosage reduction needed for renal insufficiency
- Dose Limits:
  - Pain relief
  - Intolerable side effects
  - Maximum dose of 3600 mg daily in divided doses
- Angioedema an uncommon but reported adverse reaction
Pregabalin (Lyrica)

- Same mechanism of action as gabapentin
- Approved FDA 12/31/2004
  - Schedule V
- Starting dose is 50 mg TID
  - Increase to 300 mg/day after 3-7 days
  - Maximum dose is 600 mg/day, but no evidence of added efficacy above 300 mg/day
- Dose reduction needed for renal insufficiency
- Angioedema is a potential adverse reaction
- No clear evidence of superiority of pregabalin over gabapentin
Treatment Options for Neuropathic Pain

• A combination of gabapentin and an opioid has been shown to achieve better analgesia than either drug alone

• Combined gabapentin and nortriptyline therapy has been shown to be more efficacious than either drug given alone for post-herpetic neuralgia
Other Potential Adjuvants

- Glucocorticoids (dexamethasone)
- Topicals
  - Lidocaine
  - EMLA
  - Capsaicin
- Alpha-2 agonist
  - Tizanidine
- Selective GABA-B agonist
  - Baclofen
  - Ketamine
Naloxone

Criteria for Use:
- Depressed mental status: difficult/unable to arouse
- Shallow respirations or rate less than 8/minute + evidence of inadequate ventilation (e.g. low oxygen saturation, hypotension).

Stop opioid administration.
- Dilute 0.4 mg naloxone (one amp) with NS to total volume of 10 ml (0.04 mg/mL)
- Prompt pt to breathe deep breaths
- Administer 1 ml IV (0.04 mg) q1min until the patient is responsive.
  - A typical response is noted after 2-4 ml with deeper breathing and greater level of arousal.
- If no response to 0.8 mg (2 amps), consider other causes of sedation and respiratory depression
- Repeated doses of naloxone, or even a continuous naloxone infusion, may be needed.
- Wait for sustained improvement in consciousness before restarting opioids at a lower dose

Opioid Dose Escalation

- For ongoing moderate to severe pain increase opioids doses by 50-100%, irrespective of starting dose
- For ongoing mild to moderate pain increase by 25-50%, irrespective of starting dose
- Dosage escalations of less than 25% generally have no significant efficacy.
- Short-acting oral single-agent opioids can be safely dose escalated every 2 hours (clinician supervised)
- Sustained-release oral opioids can be escalated every 24 hours.

Fast Facts #020 www.eperc.mcw.edu
Opiate Rotation

- Reduce opioid dose by 30-50% to accommodate for unknown cross-tolerance and titrate to goal.
- The wide variation among individuals is multifactorial and poorly understood.
- Incomplete cross-tolerance can lead to greater than anticipated potency in a new opioid, even though same class of analgesic is being used.
- Monitor clinical response and adverse effects.

Kishner S. Opioid equivalents Medscape
PCA

- Uses
  - Pain is escalating and not controlled with oral regimen
  - Persistent vomiting
  - Transition after procedures
  - More precise determination of opiate need
- Somnolence occurs before respiratory depression
- Basal infusion can be added once PRN use is assessed
- Typical starting dose in opiate naive pt:
  - Hydromorphone 0.1 mg IV with 12 min lockout
  - Morphine 1 mg IV with 12 min lockout
  - Fentanyl 12 mcg with 12 min lockout
- Patient or nurse activated, NOT FAMILY!
PCA Conversion

- 64 yo male, with metastatic SCC of lung with metastasis to liver, bone, and subcutaneous tissues has been on MS Contin 30 mg PO BID + 5 mg oral morphine every 2 hours PRN for breakthrough pain. In the last 24 hours he has used 5 doses of oral morphine, and presents to ED with vomiting and persistent pain that he rates 8/10. He has normal renal function and is alert. You decide to rotate to hydromorphone using a PCA.
- Calculate total OME
  - $30 + 30 + (5 \times 5) = 85 \text{ mg in 24 hour} = 3.5 \text{ mg per hour}$
- Convert to equivalent IV HYDROMORPHONE
  - $3.5 \div 20 = 0.175 \text{ mg} \times 0.7 = 0.123 \text{ mg} \Rightarrow 0.1 \text{ mg IV hydromorphone per hour}$
- PCA dose 0.1 mg hydromorphone with 12 min lockout
- Reassess pain control in 6-8 hours and adjust dose
Pain Crisis Management

- Morphine 2 mg IV initial dose
  - If no response in 10 minutes repeat 2 mg dose
  - If no response in 10 minutes, give 5 mg Q 10 min x 2 doses
  - If no response give 10 mg Q 10 minutes until pain controlled
  - Once a dose is starting to relieve pain, continue with that same bolus dose every 10 minutes until pain is 2-3/10.
- ONCE PAIN CONTROLLED: calculate total amount of opiate used
  - Give this amount over 24 hours as basal infusion with bolus dose the same mg as used for hourly infusion

- Example:
  - 2 mg + 2 mg + 5 mg + 5 mg + 10 mg morphine controls pain
  - 24 mg ÷ 24 = 1 mg/hour basal morphine infusion
  - PCA (or NCA) bolus 1 mg with 12 min lockout
  - If pain starts to escalate, ↑ infusion + bolus by 100% & reassess
IV Lidocaine in Opioid-Resistant Pain

• Randomized, double-blinded, placebo-controlled, cross over study of 50 consecutive cancer patients not responding to maximally tolerated morphine dose

• Primary end-points: Magnitude of pain relief and durability of response

• Equal volumes of NS or Lidocaine

• Lidocaine
  • 2 mg/kg bolus
  • 2 mg/kg infusion over one hour

• ECG monitoring during bolus and for 2 hrs following infusion

• Non-invasive BP and respiratory rate monitoring every 10 min

IV Lidocaine in Opioid-Resistant Pain

• Pain Types
  • 26 (52%) Mixed
  • 15 (30%) Nociceptive
  • 9 (18%) Neuropathic

### IV Lidocaine in Opioid-Resistant Pain

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time to maximal effect</td>
<td>40 min</td>
<td>75 min</td>
</tr>
<tr>
<td>Mean duration of pain relief</td>
<td>9.34 days</td>
<td>3.82 days</td>
</tr>
<tr>
<td>% of patients reporting subjective decrease in analgesic requirements in 14 day f/u observation period</td>
<td>64%</td>
<td>30%</td>
</tr>
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Summary

- Pain has sensory and emotional elements
- Pain in EOL scenarios often has nociceptive and neuropathic aspects to consider
- Effective EOL pain management utilizes opiate and non-opiate medication
- Escalating pain should be anticipated in EOL care
- Escalating pain can be effectively managed by family physicians