Long Acting Opioids
ECHO
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Disclaimer/ Objectives:

• I am not receiving any compensation from an outside entity for the delivery of this material

• Upon the completion of this brief overview and discussion the participant should be able to:
  – List opioid agents that are available in abuse deterrent long acting formulations
  – Identify patients that may be candidates for these products
  – Advocate for appropriate use of these medications
Opioid Deaths

Everyone knows that patients are dying from opioid overuse/abuse: intentional or unintentional

- Intentional - pain not controlled?
  - Suicide?
- Unintentional -
  - Benzos plus opioids - “I forgot I took it 5 times”
  - Diversion
  - Children - access to the product
  - Street medications adulterated

Concern of Opioids: SA and LA

Table 1  The 10 principles of Universal Precautions

1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy ± adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the "Four As" of pain medicine: Analgesia, Activity, Adverse Reactions, and Aberrant Behavior
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

Adapted from Gourlay et al. [1].

CDC Guideline: 12 main points

- 1- Nonpharmacologic and non opioid preferred in chronic pain
- 2- Establish treatment goals
- 3- Discuss risks and benefits
- 4- Immediate should be prescribed not LA/SR
- 5- Prescribe lowest dose possible (Avoid >90 MME/day)
- 6- Long term use begins with txt of acute pain
- 7- Evaluate at 1-4 weeks
- 8- Before continuing establish plans to mitigate risk (naloxone)
- 9- Review PDMP for use every 3 months
- 10- Consider urine drug testing
- 11- Avoid benzos with opioids
- 12- Offer txt for patients with opioid use disorder
Who is a candidate for Opioids?

**ii. Assessment of Effectiveness of Long-Term Opioid Therapy**

11. Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring. (Evidence: Level II; Strength of Recommendation: Moderate)

12. Consider up to 40 morphine milligram equivalent (MME) as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose. (Evidence: Level II; Strength of Recommendation: Moderate)

13. Avoid long-acting opioids for the initiation of opioid therapy. (Evidence: Level I; Strength of Recommendation: Strong)

14. Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses. (Evidence: Level I; Strength of Recommendation: Strong)

15. Understand and educate the patients of the effectiveness and adverse consequences. (Evidence: Level I; Strength of Recommendation: Strong)

16. Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids. (Evidence: Level I-II; Strength of recommendation: Moderate to strong)

17. Periodically assess pain relief and/or functional status improvement of $\geq 30\%$ without adverse consequences. (Evidence: Level II; Strength of recommendation: Moderate)

18. Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain. (Evidence: Level I; Strength of Recommendation: Strong)
Appropriate patient:

- Rheumatoid Arthritis?
- Osteoarthritis?
- Ankylosing spondylitis?
- Fibromyalgia?
- Back Pain?
- Chronic Noncancer Pain CNCP
Who should get Long Acting Opioids?

Who Should get Chronic Opioid Therapy

• Only after IR medications are around clock
  – Start low and escalate if needed
• Only after physical multimodality therapies
• Optimized adjunctive medications:
  – Amine uptake inhibitors
  – Gabapentenoids
  – Topical, TENS units
• No “Aberrant drug-related behaviors”
• Focus on *Functionality*
Rationale:

Serum Fentanyl Concentrations
Following Multiple Applications of DURAGESIC® 100 mcg/h (n=10)
Hydrocodone Abuse Deterrent

Zohydro: BeadTek®

Hysingla® Resistec

Figure 2. Graphic illustration of the bioavailability difference between Zohydro ER compared to IR Hydrocodone. ER, extended release; IR HC, immediate-release hydrocodone combination. ©Pernix Therapeutics. Reproduced with permission of Pernix Therapeutics.

Figure 3. Graphic illustration of the bioavailability of Hysingla ER compared with immediate-release hydrocodone bitartrate. ER, extended release; IR, immediate release. ©Purdue Pharma L.P. Reproduced with permission of Purdue Pharma L.P.
Oxycodone Long Acting

- Oxycontin®, (Generics?), Xtampza®
  - 10, 15, 20, 30, 40, 60, 80 mg Q 12
  - 9, 13.5, 18, 27, 36 mg Q 12
Opioid Use Last Ten Years

Figure 2: 10 Year Trends in Prescription Opioid Use in the Commercially Insured

Pills per Person - National

Measure
- Pills per Person

State
- National

Drug
- Tramadol
- Codeine
- Morphine
- Hydrocodone
- Oxycodone SA
- Oxycodone LA
- Fentanyl
- Other

https://www.healthcostinstitute.org/blog(entry/opioid-10yr-trends)
Abuse Deterrent Technologies: Morphine plus Naltrexone:

EMBEDA is specifically designed with sequestered naltrexone HCl, which is released with manipulation by crushing. EMBEDA capsules contain pellets of ER morphine sulfate and sequestered naltrexone HCl.

The role of sequestered naltrexone HCl in EMBEDA: When taken as directed, the sequestered naltrexone is intended to have no clinical effect.

Oxycodone plus naltrexone: Troxyca ER® Approved 8/19/16 Pfizer stopped sales 8/16/19 Elite Pharm Looking to obtain rights to market.
Methadone:

- CAN be prescribed for pain!
- VERY long t½ half
- 5,10mg (40mg) tablets
- Figure out dose-
- Give ½ for 1 week
- “Document that you told them and they understand NOT to take methadone for BT pain!”
  - BT = Break Through
- Give whatever for that
- Up your basal after week

- Conversion Ratio of Oral Morphine to Oral Methadone
- <100 mg - 3:1 (i.e., 3 mg morphine:1 mg methadone)
- 101-300 mg - 5:1
- 301-600 mg - 10:1
- 601-800 mg - 12:1
- 801-1000 mg - 15:1
- >1001 mg - 20:1
- Due to incomplete cross-tolerance, it is recommended that the initial dose is 50-75% of the equianalgesic dose.
Seattle Times Methadone Deaths

Consumption of methadone in Washington state, in grams, from 1997 to 2006

Accidental methadone deaths in Washington from 1999 to 2010

Cost comparison: OxyContin costs the state more than 12 times as much as a comparable amount of methadone.

Source: U.S. Drug Enforcement Administration; Seattle Times analysis of Washington death-certificate data; Department of Social and Health Services
The End

Completeness slides and interesting data if time permitting:
Fentanyl: Topical Good, Buccal Bad

- Duragesic®, Generics
  - 12,25,50,75,100 mcg/hour- 72 hour patch
  - Disposal!

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**TABLE 1: DOSE CONVERSION GUIDELINES**

<table>
<thead>
<tr>
<th>Current Analgesic</th>
<th>Daily Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine</td>
<td>60-134 135-224 225-314 315-404</td>
</tr>
<tr>
<td>Intramuscular or Intravenous</td>
<td>10-22 23-37 38-52 53-67</td>
</tr>
<tr>
<td>morphine</td>
<td></td>
</tr>
<tr>
<td>Oral oxycodone</td>
<td>30-67 67.5-112 112.5-157 157.5-202</td>
</tr>
<tr>
<td>Oral codeine</td>
<td>150-447</td>
</tr>
<tr>
<td>Intravenous hydromorphone</td>
<td>1.5-3.4 3.5-5.6 5.7-7.9 8-10</td>
</tr>
<tr>
<td>Intramuscular meperidine</td>
<td>75-165 166-278 279-390 391-503</td>
</tr>
<tr>
<td>Oral methadone</td>
<td>20-44 45-74 75-104 105-134</td>
</tr>
</tbody>
</table>

Recommended DURAGESIC Dose
- 25 mcg/hour
- 50 mcg/hour
- 75 mcg/hour
- 100 mcg/hour

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**TABLE 2: RECOMMENDED INITIAL DURAGESIC DOSE BASED UPON DAILY ORAL MORPHINE DOSE**

<table>
<thead>
<tr>
<th>Oral 24-hour Morphine (mg/day)</th>
<th>DURAGESIC Dose (mcg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
</tr>
<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
<tr>
<td>405-494</td>
<td>125</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
<tr>
<td>585-674</td>
<td>175</td>
</tr>
<tr>
<td>675-764</td>
<td>200</td>
</tr>
<tr>
<td>765-854</td>
<td>225</td>
</tr>
<tr>
<td>855-944</td>
<td>250</td>
</tr>
<tr>
<td>945-1034</td>
<td>275</td>
</tr>
<tr>
<td>1035-1124</td>
<td>300</td>
</tr>
</tbody>
</table>

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC.

1. Table 1 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible [see Dosage and Administration (2.3)].

2. Calculate the previous 24-hour analgesic requirement.
3. Convert this amount to the equianalgesic oral morphine dose using a reliable reference.
Tapentadol Nucynta®

- Mu- opioid receptor agonist
- Norepinephrine reuptake inhibitor
- 50, 75, 100 mg tablets NMT 600/day
- 100, 150, 200 mg SR
- Oral bioavailability 32%, T ½ 4 hours
- 97% hepatic metabolism Renal elimination
- Analgesia comparable to:
  - Oxycodone, Morphine
Buprenorphine Butrans

- Once weekly Schedule III
- Low to Moderate potency
- 5,10,15,20 mcg/hour

~ Belbuca, Probuphine, and Buprenex are other buprenorphine brands
Are they really “Abuse Deterrent”

Fig. 1 Photos of intact and manipulated opioids. The tool that was most effective at crushing each product was used for manipulated products.

In Vitro Drug Release After Crushing: Evaluation of Xtampza® ER and Other ER Opioid Formulations
Stephen P. Mayock, Said Saim, Alison B. Fleming
Long Acting Agonist Antagonist

• Naltrexone: Antagonists
  – Indicated for Alcohol Abstinence
  – Indicated for Opioid Abstinence
  – Orally: Daily
    • Revia, Generics 50 mg
    • Depo Injection: Vivitrol

• Buprenorphine: Agonists/Antagonist
  – Implants: Probuphine
    • 4 Implants Q 6 Months
  – Depo Injection: Sublocade
    • Induction, 300,300,100 Q month