Buprenorphine

Addiction and chronic pain management

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Disclosures

Relevant Financial Relationships
None

Off-label Investigational Uses
None
Learning Objectives

• Review the basic formulations, dosing, and side-effects of buprenorphine

• Identify differences in buprenorphine prescribing between the indications of addiction management and chronic pain

• Understand the evidence for the use of buprenorphine in chronic pain
History of buprenorphine in the U.S.

1985 - Initial marketing as analgesic in 1985

2002 – FDA approved for addiction management

2010 – FDA approved transdermal formulation for chronic pain management

2015 – FDA approved buccal buprenorphine for chronic pain management

2016 – FDA approved implantable buprenorphine product for addiction maintenance
Business is booming

- 2015 – sales of daily oral formulations of buprenorphine totaled $2 Billion

- Since 2006, more prescriptions of buprenorphine than methadone

1 http://www.titanpharm.com/pipeline/probuphine
Just the facts…

• Partial agonist of the mu opioid receptors

• Also,
  • Weak antagonist of Kappa opioid receptors
  • Agonist of delta opioid receptors
  • Partial agonist of ORL-1 (nociceptin)

• Hepatic metabolism

• BILIARY and renal excretion

• Terminal ½ life ~ 26 hours
Buprenorphine

• Formulations
  • US availability
    • Buprenorphine alone
      • Subutex (sublingual tab – generic only)
      • _____________ (transdermal patch)
      • _____________ (buccal film)
      • _____________ (injectable)
      • _____________ (implantable)
    • Formulations combined with naloxone
      • _____________, _____________, _____________
Outline

- Introduction
- Indications
- Dosing and titration
- Weaning
- Side effects
- Effectiveness
- Conclusion
Addiction Maintenance

• Buprenorphine-naloxone formulations – FDA approved 2002

• Buprenorphine CAN be abused

• After DATA 2000, special licensure from SAMHSA and DEA
  • “X” DEA number issued for this purpose
    • Fully searchable online
  • Special training
  • Patient quota
Implantable Buprenorphine

- Recent approval for addiction maintenance
- 4 probuphine implants are inserted subdermally in the upper arm
- Left in place for 6 months
- Must be removed

- Not for initial therapy. Patient must have “sustained prolonged clinical stability on transmucosal buprenorphine.”

1. Probuphine Full Prescribing Information
Implantable Buprenorphine
Implantable Buprenorphine

The curved tip of the X-plant clamp fits around the implant.
Implantable Buprenorphine

- Better than traditional sublingual route?

- Trial
  - Randomized
    - Implantable vs. sublingual
    - 96.4% vs 87.6% maintained abstinence
    - Result – Non-inferiority!

Chronic Pain Management

- ________ - FDA approval 2010
- ________ - FDA approval 2015
  - Moderate to severe pain requiring long term treatment
  - Ineffective alternatives

- Contraindications:
  - Significant respiratory depression
  - Severe bronchial asthma
  - Paralytic ileus
  - Anaphylaxis
Buprenorphine for Chronic Pain

Advantages

• Less addiction potential?
• Ceiling for respiratory depression?
• Easy administration – improved compliance
• No significant QTc effects
• Reliable elimination

Disadvantages

• There remains opioid abuse potential
• Cost
• Induced withdrawal
• Perioperative concerns
Perioperative Problem

- Highly bound to opioid receptor
- Traditional post-operative analgesics don’t have access to receptors
- Long half-life
- If present, standard opioid therapy will be less efficacious
- Problem often not addressed pre-operatively
Perioperative Solutions

• Elective
  • Stop 3-5 days pre-operatively and replace with traditional opioid agonist
  • Cancel/delay case?

• Urgent/Emergent
  • Stop on arrival (Probuphine?)
  • Supplement with high dose opioids and monitoring
    • Watch for sedation as buprenorphine dissociates
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Dosing and Titration - Butrans

- **Opioid Naïve**
  - Start with 5 mcg/hr patch

- **Opioid Experienced**
  - Less than 30 OME
    - 5 mcg/hr patch
  - Between 30 and 80 OME
    - 10 mcg/hr patch
  - Greater than 80 OME
    - Consider alternatives
Dosing and Titration - Belbuca

• Opioid Naïve
  • Start with 75 mcg daily (titrating to BID)

• Opioid Experienced
  • Less than 30 OME
    • 75 mcg daily (titrating to BID)
  • Between 30 and 89 OME
    • 150 mcg q 12 hours
  • Between 90 mg to 160 mg
    • 300 mcg q 12 hours
Special Populations

Renal Disease

- No relationship between CrCl and steady plasma drug concentrations

Hepatic Disease

- No increased exposure to parent drug or metabolites in patients with Child-Pugh A or B liver disease
- There is increased exposure in moderate to severe disease\(^1\)
- Use with caution

## Things to tell your patient about the patch...

### Do
- Rotate application sites
- Apply to upper arm, back, chest
- Discuss possibility of problems with pain control peri-operatively

### Don’t
- Repeat application site for 4 weeks
- Heat the patch
- Cut the patch
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Weaning

- Consider indication for medication
  - Chronic pain – relatively low doses
    - Decrease in step-wise fashion
- Addiction
  - Need specialized training
  - Slow wean\(^1\)
  - ~ 25% every 10 days
  - Likely will experience withdrawal

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Side Effects

Common
• Nausea
• Headache
• Dizziness
• Drowsiness

Uncommon
• Respiratory depression
• Hypotension

The peri-operative conundrum
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Low Back Pain

• Sublingual for chronic back pain\(^1\)
  • Vs. placebo

• Improved activities of daily living\(^2\)

• Improved pain and disability scores\(^3\)


Neuropathic Pain

• Cochrane Review
  • No studies met inclusion criteria\(^1\)
  • Thereby, no recommendation

• Diabetic neuropathy\(^2\)
  • Slight benefit to sham
  • High drop-out rate

Cancer Pain

• Cochrane Review
  • Mixed results. Very low quality data.\(^1\)

• Meta-analysis for transdermal delivery and cancer\(^2\)

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Conclusions

• Transdermal buprenorphine and buccal buprenorphine is FDA approved for moderate-severe chronic pain

• Patient selection, as with all opioid therapy, is vital

• Limited trials available, but evidence suggests safety and efficacy for select indications
Thank You

Questions?

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