2002 to 2017: The Evolution of Buprenorphine Treatment

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Disclosures

- Royalties from American Psychiatric Publishing, Inc. for “Office-Based Buprenorphine Treatment of Opioid Dependence.”

The contents of this activity may include discussion of off-label or investigational drug uses.
Target Audience

• The overarching goal of PCSS-O is to offer evidence-based trainings on the safe and effective prescribing of opioid medications in the treatment of pain and/or opioid addiction.

• Our focus is to reach providers and/or providers-in-training from diverse healthcare professions including physicians, nurses, dentists, physician assistants, pharmacists, and program administrators.
Educational Objectives

• At the conclusion of this activity participants should be able to:
  ▪ Explain changes in patterns of opioid use disorder since 2002
  ▪ Describe regulatory changes relevant to buprenorphine in DATA 2000 and CARA 2016
  ▪ Describe changing standards of care in the use of buprenorphine in the treatment of opioid use disorder
Outline

• Changing patterns of opioid use disorder
• Regulatory changes
• Induction protocols; Treatment dose range
• Clinical management:
  • Counseling
  • Diversion control plans
• Treating pregnant patients: The Mother Study
• Hepatotoxicity: The START Study
• Managing acute & chronic pain
• Maintenance vs. Detoxification: The Kakko Study
• Morbidity & Overdose Prevention: The Sordo Study
<table>
<thead>
<tr>
<th>Natural (from opioids 100%)</th>
<th>Semi-synthetic (derived from opium)</th>
<th>Synthetic (man made)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Buprenorphine</td>
<td>Meperidine</td>
</tr>
<tr>
<td>Morphine</td>
<td>Hydromorphone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Thebaine</td>
<td>Oxycodone</td>
<td>Propoxyphene</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone **</td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Hydrocodone</td>
<td>Tramadol</td>
</tr>
</tbody>
</table>
Heroin Use and Non-Medical Use of Pain Relievers in the Past Year among Persons Aged 12 or Older: 2002-2013

Persons Aged 12 or Older

Non-medical users of pain relievers

Heroin users

NSDUH, 2014
Fentanyl deaths on the rise

PERCENT OF OPIOID DEATHS WITH SPECIFIC DRUG PRESENT

Massachusetts, 2014-16

80%

SOURCE: Massachusetts Department of Public Health

GLOBE STAFF
Regulatory Changes: DATA 2000, CARA 2016 & SAMHSA

- Practice limits: 30 to 100 to 275
- Special requirements to treat between 100 to 275 patients:
  - Applicant must be a board-certified addiction specialist
  - OR
  - Applicant must work in a “Qualified Practice Setting” that
    - Provides case management and related services
    - Is registered with the State PDMP
    - Provides 24 hours emergency coverage
    - Uses established practice guidelines for OUD
    - Uses health information technology (EHRs)
    - Accepts third party payment for some services
Regulatory Changes: DATA 2000, CARA 2016 & SAMHSA

• Authorization for Physician Assistants & Nurse Practitioners to prescribe; 24 hours required training (CARA Legislation)

• Current DHHS/SAMHSA Regulations:
  ➢ Buprenorphine in an Opioid Treatment Program – permits flexible prescribing if clinician is waivered
  ➢ Expect clinicians to utilize Diversion Prevention Plans

• Enhanced prescriber training requirements (8 hour courses):
  ➢ Extended-release Naltrexone
  ➢ Methadone
  ➢ Pain management (in some states)
Buprenorphine Formulations

- Sublingual buprenorphine/naloxone tablet
  - New film strip formulation in 2010
  - Generic sublingual formulations 2013
  - New brand formulations
- Extended release subdermal rods 2016

- Over 400,000 patients currently in active treatment
# Buprenorphine - Equivalent Doses

<table>
<thead>
<tr>
<th>Generic Tablets</th>
<th>Suboxone® Film</th>
<th>Zubsolv® Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mg/0.5mg</td>
<td>2mg/0.5mg</td>
<td>1.4mg/0.36mg</td>
</tr>
<tr>
<td>8mg/2mg</td>
<td>8mg/2mg</td>
<td>5.7mg/1.4mg</td>
</tr>
<tr>
<td>One 8mg/2mg plus Two 2mg/0.5mg</td>
<td>12mg/3mg</td>
<td>5.7mg/1.4mg plus Two 1.4mg/0.36mg</td>
</tr>
<tr>
<td>Two 8mg/2mg</td>
<td>16mg/2mg</td>
<td>Two 5.7mg/1.4mg</td>
</tr>
</tbody>
</table>
Bunavail® Buccal Film

Available dosages (BUP/NX): 2.1 mg / 0.3 mg; 4.2 mg/0.7 mg; 6.3 mg/1.0mg

Recommended maintenance dose: 8.4mg / 1.4mg
Buprenorphine Induction Protocol

- Patient must show signs of mild-moderate opiate withdrawal
- Use Clinical Opiate Withdrawal Scale or Objective Opiate Withdrawal Scale to quantify withdrawal
- Begin with 2/0.5 or 4/1 mg buprenorphine/naloxone
- Can re-dose in 2 hours if opiate withdrawal is not diminished by first dose
- 8/2 mg first day target dose
- Return to clinic to re-evaluate next day; increase dose if indicated
- Most stabilize on 12/3-16/4 mg daily
- FDA approved dose range is up to 24/6 mg daily
Buprenorphine Outpatient Induction Recommendations

• Abstinence prior to first BUP/NX dose:
  - 16 hrs for short-acting opioids (heroin)
  - 24 hrs for sustained-release opioid medications
  - 36 hrs for methadone (30mg x 2 weeks; 15mg x 1 day; no methadone x 1 day; then induce on BUP/NX)

• COWS score 8-10 before 1st dose (2 or 4 mg)
• For patients abusing fentanyl, a COWS score of 13-15 may be safer target to avoid precipitated withdrawal

• Rapid escalation to 12mg, if needed, by end of day 2

Buprenorphine – Induction Recommendations

- Home induction can be considered for reliable patients with prior experience taking buprenorphine
- Monitor progress with telephone calls
- Weekly office visits until stable in treatment
Opioid Use Disorder: Additional Treatment Components

• Psychosocial Services
  ▪ Case management
  ▪ Individual and group therapy
  ▪ Family therapy
  ▪ 12 Step/Mutual Support Groups
  ▪ Higher psychiatric severity patients more responsive to increased services

• Contingency treatments very useful
  ▪ E.g.: More extended prescriptions
The Role of Counseling

- Standard recommendations since 1965 have stressed the importance of ancillary counseling for success in opioid agonist therapy

- Benefits are well documented by research – Ball & Ross, 1991; McLellan, 1993

- Two recent buprenorphine trials suggest that brief, frequent physician medication monitoring visits are equal to, if not more effective than more intensive drug counseling – Fiellin, 2006; Weiss, 2011
Opioid Use Disorder: Urine Toxicology Screening

- Random Urine Toxicology Screening: Gold standard and must be utilized in substance use disorder

- Heroin is excreted in urine as morphine

- 6-monoacetyl morphine (6-MAM) detected for 12 hours – evidence of recent heroin use

- Routine screens show morphine, codeine, 6 MAM; will not detect meperidine, oxycodone, fentanyl, tramadol, buprenorphine, methadone, hydrocodone

- Poppy seeds contain trace amounts of codeine and morphine. Even small amounts of poppy seeds can give positive urine morphine test; 2000 ng/ml cutoff
Buprenorphine: Recommendations for Minimizing Diversion and Drug Misuse

- Use BUP/NX for all patients except pregnant women
- Whenever possible keep dose to 16/4 mgs or below
- After initial stabilization, wait at least 5-7 days to assess benefit of any dose increase
- Over 16/4 mg, emphasize psychosocial techniques to manage ongoing craving or use
- Weekly physician visits until stable
- Regular urine toxicology screens
- Regular check of state Prescription Drug Monitoring Program
- Call-backs for pill counts and tox screens, as needed
- Dose reductions to 8/2 mg for long-term stable patients
- Encourage AA / NA
Opioid Replacement Therapy in Pregnancy and in the Neonatal Period

• Methadone maintenance is considered the gold standard and strongly advised; BUP shown to be effective as well (Jones et al. 2010)
  ➢ Removes mother from drug-using environment
  ➢ More likely to get prenatal obstetrical care
  ➢ Reduces obstetrical complications
  ➢ Improves maternal/fetal nutrition
  ➢ Increases birth weight

• Need structure and psychosocial support

• Opioids not teratogenic
• Convert buprenorphine/naloxone to buprenorphine if woman wants to continue buprenorphine treatment

• **MOTHER study** showed: Higher dropout with BUP (33%) v. methadone (18%); not an issue in other studies

• Neonatal Abstinence Syndrome often occurs (in up to 90% of infants and 50% will need treatment):
  - Irritability, fever, diarrhea, hyperreflexia, seizure
  - Treatment: Tincture of opium, morphine
  - Methadone NAS resulted in significantly longer hospital stay than for infants of BUP treated women (9.9 vs. 4.1 d) (p=0.003); no difference in rates of NAS; just less severity

Neonatal Abstinence Syndrome

Opioid Use Disorder and Pregnancy

- Methadone and buprenorphine are excreted into breast milk
- Breastfeeding should be encouraged unless there are other conditions that would be a contraindication
- Methadone in breast milk may help with NAS
- Buprenorphine in breast milk not well absorbed; not likely to help with NAS
Side Effects

- Buprenorphine’s primary side effects are similar to other mu agonist opioids such as methadone (e.g., nausea, constipation, decreased libido), but symptoms may be less severe.
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance.
- No evidence of hepatotoxicity or other organ damage with chronic dosing.
Interactions: Cytochrome P450 3A4

• **3A4 Inhibitors** might raise buprenorphine levels.
  • Azole antifungals, Macrolide antibiotics, Protease inhibitors inhibit buprenorphine N-dealkylation *in vitro*.
  • Significant increase in buprenorphine/norbuprenorphine exposure with atazanavir
    • possible side effect of sedation
    • one case report of cognitive impairment in 3 patients with HIV treated with both drugs

• **3A4 Inducers** might lower buprenorphine levels.
  • Phenobarbital, Carbamazepine, Phenytoin, Rifampin
  • Efavirenz

• An extensive list can be found in TIP 40 & at [www.drug-interactions.com](http://www.drug-interactions.com)
Case reports – IV administration of high acute doses of buprenorphine in patients with history of hepatitis:

Four case reports of hepatitis: Transaminases increased, 13-50x normal, with IV buprenorphine in patients infected with Hepatitis C.

Mechanism: Buprenorphine inhibits hepatic mitochondrial function at high concentrations.

This magnitude of effect should not occur with sublingual administration.
The Food and Drug Administration (FDA) requested a study comparing buprenorphine/naloxone (BUP/NX) and methadone (MET) on indices of hepatic safety. Compare changes in liver enzymes related to treatment with BUP/NX to changes in liver enzymes related to treatment with MET. Identify risk factors at baseline and during treatment that could contribute to interactions with BUP/NX or MET causing liver dysfunction. Assess abstinence from illicit substances. Assess abstinence from alcohol.

## START Study: Main Liver Outcomes

<table>
<thead>
<tr>
<th>AST and ALT</th>
<th>BUP/NX (n=340)</th>
<th>MET (n=391)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2X ULN remain ≤2X ULN</td>
<td>273 (80.3%)</td>
<td>306 (78.3%)</td>
</tr>
<tr>
<td>≤2X ULN then ↑ &gt;2X ULN</td>
<td>43 (12.6%)</td>
<td>70 (17.9%)</td>
</tr>
<tr>
<td>&gt;2X ULN then ↓ ≤2X ULN and remain ≤2X ULN</td>
<td>11 (2.4%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>&gt;2X ULN do not ↓ ≤2X ULN or ↑ &gt;2X eligibility value</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>&gt;2X then ↑ &gt;2X eligibility value</td>
<td>9 (2.6%)</td>
<td>6 (1.5%)</td>
</tr>
</tbody>
</table>
Liver Function Tests

Check at baseline, prior to starting buprenorphine treatment.

- If normal, then follow periodically.
- If mildly elevated (<3x normal), follow every 1-2 months until confident they are stable
- If markedly elevated, follow closely.

Special thanks to A. Saxon and START Study research group
Buprenorphine and Acute Pain

- Acute pain in buprenorphine patients
  - Bup blocks most mu agonists - may depend on dose
  - May be a challenge to provide adequate analgesia
  - Consider non-opioid alternatives first line
  - Moderate pain consider buprenorphine in divided doses (6 to 8 hours schedule), if that is inadequate, **ADD**:
    - Concurrent short-acting opioid analgesic, **OR**
    - Supplemental low dose buprenorphine (2/0.5 mg) BID

- Watch for relapse risk. Use short term prescriptions and coordinate care
Buprenorphine and Acute Pain

• **Severe Acute Pain** in the inpatient setting:

  - Stop buprenorphine and convert to a long-acting full agonist (may do this on the morning of surgery)

  - Methadone 30-40 mg po daily or extended-release morphine 15mg BID to manage daily opioid requirement

  - Add concurrent short-acting opioid for analgesia

  - Naloxone (Narcan) at the bedside

  - Convert back to Buprenorphine before discharge
Opioid Use Disorder and Chronic Pain

- Limited evidence of usefulness of long term opioid therapy for chronic, non-malignant pain
- Treatment Agreement /Informed Consent (documentation of risk/benefit) advised; Treatment Agreement to stipulate:
  - One physician/one pharmacy
  - Urine Drug Screens when requested
  - Agreement to return for pill count when asked to do so
  - Medication Levels
  - Number/frequency of all refills
  - Reason for discontinuation (violation of agreement, misuse of medication, misuse of other substances)
- Chronic pain with opioid addiction may do better with methadone
- More moderate chronic pain may do better with buprenorphine in divided doses
Buprenorphine Maintenance vs. Detoxification

- Double-blind, random assignment to:
  - 16 mg/day SL buprenorphine tablets, or
  - 6 day buprenorphine detoxification followed by placebo
- First week of study was inpatient.
- Study lasted one year.
- Take home doses were allowed after 6 months of treatment.

Kakko, Lancet, 2003
Buprenorphine Maintenance vs. Detoxification

All participants also received psychosocial treatments:

- Group therapy
- Individual counseling
- Assistance with housing
- Assistance with employment
Maintenance vs. Detoxification: Retention: Kakko, Lancet 2003
### Maintenance vs. Detoxification: Mortality

<table>
<thead>
<tr>
<th></th>
<th>Detox/Placebo</th>
<th>Buprenorphine</th>
<th>Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>4/20 (20%)</td>
<td>0/20 (0%)</td>
<td>$\chi^2=5.9; p=0.015$</td>
</tr>
</tbody>
</table>

Buprenorphine Maintenance vs. Detoxification

• Studies show (a) the efficacy of maintenance treatment, and (b) the poor outcomes associated with taper/detoxification.

• Medication withdrawal treatment results in poor outcomes even when provided with psychosocial treatments including hospitalization, cognitive behavioral therapy, and help with social service agencies.
Overdose With Buprenorphine

- Pre-clinical studies suggest that high doses of buprenorphine should not produce respiratory depression or other significant problems.
- We have no reports of respiratory depression in clinical trials comparing buprenorphine to methadone.
- Overdose of buprenorphine combined with other CNS depressants may cause problems.
- All patients should be provided naloxone rescue kits.
Overdose and Misuse Potential

- Buprenorphine in all forms (SL, SQ, IM, IV) has relatively lower misuse risk than full agonists.
- Parenteral buprenorphine is misused. Epidemiological studies in a variety of countries and human laboratory studies both demonstrate that injectable buprenorphine is reinforcing and misused.
- Addition of naloxone to sublingual buprenorphine reduces risk of misuse and overdose.
Mortality Risk During & After Opioid Agonist Treatment

- Cohort study following 122,885 methadone patients
- Compared to 15,831 buprenorphine patients
- Minimum treatment 1.3 years
- Significant reduction in all cause and overdose mortality compared to addicts not in treatment
- Higher risk during 1st month on methadone and after taper from either medication

Treatment Costs Opiate Dependent Patients

Total Cost/Opiate Dependent Patient in 6 months post

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost per patient $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depot NTX</td>
<td>8582</td>
</tr>
<tr>
<td>Oral NTX</td>
<td>8903</td>
</tr>
<tr>
<td>Bupe</td>
<td>10049</td>
</tr>
<tr>
<td>Meth</td>
<td>16752</td>
</tr>
<tr>
<td>Drug-free</td>
<td>14353</td>
</tr>
</tbody>
</table>

Questions?

john.renner@va.gov
PCSS-O Colleague Support Program and Listserv

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.

- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.

- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: 
www.pcss-o.org/colleague-support

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org.
PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: Addiction Technology Transfer Center (ATTC), American Academy of Neurology (AAN), American Academy of Pain Medicine (AAPM), American Academy of Pediatrics (AAP), American College of Physicians (ACP), American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), International Nurses Society on Addictions (IntNSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: [www.pcss-o.org](http://www.pcss-o.org)
For questions email: pcss-o@aaap.org

Twitter: [@PCSSProjects](https://twitter.com/PCSSProjects)

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