Using Buprenorphine to Treat Acute Opioid Withdrawal in the ED

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- Relationships with Commercial Interests:
  - Speakers honoraria: Reckitt Benckiser
  - Administrative salary from the Royal Alexandra Hospital Foundation through Alberta Health Services

- Potential for Conflicts of Interest:
  - Dr. Karine Meador has received a speakers honorarium from Reckitt Benckiser whose products are being discussed in program
Mitigating Potential Bias

- Recommendations are based on best available evidence
One doctor thought I was just another junkie looking for pills.

Methadone Saves Lives.ca

Treatment
Counseling
Support

METHADONE SAVES LIVES
Buprenorphine vs. Methadone

Perception?

VS.
Buprenorphine vs. Methadone

Reality!

VS.
Objectives

- To look at the pharmacology of buprenorphine and understand how it can act as both a partial opioid agonist and an opioid antagonist
- To learn how and when buprenorphine can be used to treat acute opioid withdrawal
- To review some of the protocols for the use of buprenorphine in acute withdrawal being used across Canada
- To look at a specific case where buprenorphine was successfully used to treat opioid withdrawal in the emergency department
Rates of opioid addiction and overdose are increasing in Canada. From 2005/06 to 2010/11, there was an almost 250% increase in the number of ED visits in Ontario related to narcotic withdrawal, overdose, intoxication, psychosis, harmful use, and other related diagnoses. The mainstay of treatment for opioid addiction remains agonist treatment with either methadone or buprenorphine - lack of access leads to many people seeking help in the ED instead.

Opioid Withdrawal

- Physical symptoms; “flu-like”, myalgias, abdominal cramps, diarrhea, nausea, chills
- Psychological symptoms; anxiety, cravings, insomnia, fatigue, depression
- Objective signs; lacrimation, rhinitis, yawning, sweating, piloerection, restlessness, uncomfortable, mild tachycardia/hypertension
- Risks; relapse, overdose, suicide, miscarriage/premature labour
Opioid Withdrawal

- Physical symptoms peak at 2-3 days after last use and resolve by 5-10 days
- Symptomatic treatment: clonidine, imodium, antiemetic, acetaminophen/NSAIDs, benzodiazepines
- Replacement treatment: methadone, buprenorphine, other opioids
Buprenorphine

- First marketed in the 1980’s as an analgesic (sublingual and injectable)
- Approval of sublingual buprenorphine for treatment of opioid addiction
  - USA - 2002
  - Europe - 2006
  - Canada - 2007
Pharmacology

- Synthetic opioid
- Partial agonist of the mu-opioid receptor (analgesia, sedation, euphoria, respiratory depression, miosis, decreased bowel motility)
- Antagonist of the kappa-opioid receptor (unknown clinical relevance, antidepressant properties)
- Very high affinity for the mu-opioid receptor; will displace other full opioid agonists or block their action
Ceiling Effect

- Because of the low intrinsic activity at the mu receptor, as the dose is increased, the agonist effect does not increase.
- Higher doses occupy a greater number of receptors but do not produce increasing opioid effects.
- A maximum effect is reached, regardless if the dose continues to increase (24mg-32mg).
- Overdose is less likely to cause fatal respiratory depression.
Overdose

- Concomitant use of sedating agents such as benzodiazepines or CNS depressants (e.g., alcohol) creates additive effects of the sedative properties of buprenorphine.

- Some cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, or other depressants such as alcohol or other opioids.
Side Effects

- Generally well tolerated
- Headache, constipation, sweating most common
- Less sexual side effects than methadone
- Less risk of QTc prolongation than methadone
Pharmacokinetics

- **Onset of action**
  - Onset of action within 30-60 minutes
  - Peak occurs within 1-4 hours

- **Duration of action**
  - Slow dissociation from receptors
  - Duration is dose dependent but can be up to 72 hours
Formulations

- Subutex; sublingual, buprenorphine

- Suboxone; sublingual, buprenorphine and naloxone (opioid antagonist) in a 4:1 ratio
  - Naloxone is not significantly bioavailable when taken sublingually or when swallowed
  - Active when used intravenously (to help fight diversion and injection use)
Canada

- **Suboxone**

- Generic buprenorphine/naloxone now also available in Canada
- Subutex only available through Health Canada’s Special Access Program for pregnant patients
- Requirements for prescribing varies across provinces
Prescribing Requirements

Provinces without restriction:

- Ontario (Recommended completion of course on buprenorphine or training in treating opioid use disorders, completion of clinical observership in an opioid dependency clinic, ongoing continuing medical education in addiction medicine, obtaining of a methadone exemption)
- Prince Edward Island (Recommended completion of course on buprenorphine)
Prescribing Requirements

Provinces where a methadone exemption is required:

- British Columbia
- Saskatchewan
- Manitoba
- New Brunswick (or experience in the treatment of opioid use disorders)
- Nova Scotia
- Newfoundland and Labrador

- BC, Saskatchewan, Manitoba, and Newfoundland and Labrador also require completion of buprenorphine prescribing training
Prescribing Regulations

Provinces where extra training is required:

- Quebec (Experience in treatment opioid use disorders or completion of training program on prescribing buprenorphine)
- Alberta (Initiation - experience in treatment of opioid use disorders and accredited buprenorphine course, Maintenance - accredited buprenorphine course and relationship with physician experienced in treatment of opioid dependence)
Further Restrictions

- Alberta is the only province with open coverage of buprenorphine
- No coverage in Manitoba
- All other provinces only provide coverage if methadone is contraindicated (patients at a high risk of QTc prolongation or a hypersensitivity to methadone) or if there has been an inadequate response to methadone
- Ontario, Saskatchewan, and Quebec will provide coverage when a methadone maintenance program is not available or accessible
- NIHB now also providing coverage
Efficacy as Agonist Treatment


- Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials.
- If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use).
- Buprenorphine retains fewer people than methadone when doses are flexibly delivered and at low fixed doses.
Efficacy in Treatment of Withdrawal


- Buprenorphine is more effective than clonidine or lofexidine in reducing the signs and symptoms of opioid withdrawal, retaining patients in withdrawal treatment, and supporting the completion of treatment.

- No significant difference in the incidence of adverse effects, but patients treated with buprenorphine may be less likely to drop-out due to adverse effects than is the case with clonidine or lofexidine.

- Buprenorphine may offer some advantages over methadone, at least in inpatient settings, in terms of quicker resolution of withdrawal symptoms and possibly slightly higher rates of completion of withdrawal.
Buprenorphine Initiation

- Wait for moderate opioid withdrawal

- Depending on the opioid and route of administration, can range from 8-36 hours after last use (for methadone it can be as long as 72+ hours)

- Objective scale: COWS (score >12)
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient’s signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

<table>
<thead>
<tr>
<th>Patient’s Name:</th>
<th>Date and Time <strong>/</strong>/__ : ___</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reason for this assessment:</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Resting Pulse Rate:</strong></th>
<th>GI Upset: over last ½ hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured after patient is sitting or lying for one minute</td>
<td>0 no GI symptoms</td>
</tr>
<tr>
<td>0 pulse rate 80 or below</td>
<td>1 stomach cramps</td>
</tr>
<tr>
<td>1 pulse rate 81-100</td>
<td>2 nausea or loose stool</td>
</tr>
<tr>
<td>2 pulse rate 101-120</td>
<td>3 vomiting or diarrhea</td>
</tr>
<tr>
<td>4 pulse rate greater than 120</td>
<td>5 Multiple episodes of diarrhea or vomiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sweating:</strong></th>
<th>Tremor observation of outstretched hands</th>
</tr>
</thead>
<tbody>
<tr>
<td>over past ½ hour not accounted for by room temperature or patient activity</td>
<td>0 No tremor</td>
</tr>
<tr>
<td>0 no report of chills or flushing</td>
<td>1 tremor can be felt, but not observed</td>
</tr>
<tr>
<td>1 subjective report of chills or flushing</td>
<td>2 slight tremor observable</td>
</tr>
<tr>
<td>2 flushed or observable moistness on face</td>
<td>4 gross tremor or muscle twitching</td>
</tr>
<tr>
<td>3 beads of sweat on brow or face</td>
<td></td>
</tr>
<tr>
<td>4 sweat streaming off face</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Restlessness:</strong></th>
<th>Yawning Observation during assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation during assessment</td>
<td>0 no yawning</td>
</tr>
<tr>
<td>0 able to sit still</td>
<td>1 yawning once or twice during assessment</td>
</tr>
<tr>
<td>1 reports difficulty sitting still, but is able to do so</td>
<td>2 yawning three or more times during assessment</td>
</tr>
<tr>
<td>3 frequent shifting or extraneous movements of legs/arms</td>
<td>4 yawning several times/minute</td>
</tr>
<tr>
<td>5 Unable to sit still for more than a few seconds</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pupil size:</strong></th>
<th>Anxiety or Irritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 pupils pinned or normal size for room light</td>
<td>0 none</td>
</tr>
<tr>
<td>1 pupils possibly larger than normal for room light</td>
<td>1 patient reports increasing irritability or anxiousness</td>
</tr>
<tr>
<td>2 pupils moderately dilated</td>
<td>2 patient obviously irritable anxious</td>
</tr>
<tr>
<td>5 pupils so dilated that only the rim of the iris is visible</td>
<td>4 patient so irritable or anxious that participation in the assessment is difficult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bone or Joint aches:</strong></th>
<th>Gooseflesh skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</td>
<td>0 skin is smooth</td>
</tr>
<tr>
<td>0 not present</td>
<td>3 pilorrecrion of skin can be felt or hairs standing up on arms</td>
</tr>
<tr>
<td>1 mild diffuse discomfort</td>
<td>5 prominent pilorrecrion</td>
</tr>
<tr>
<td>2 patient reports severe diffuse aching of joints/muscles</td>
<td></td>
</tr>
<tr>
<td>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Runny nose or tearing:</strong></th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not accounted for by cold symptoms or allergies</td>
<td>The total score is the sum of all 11 items</td>
</tr>
<tr>
<td>0 not present</td>
<td>Initials of person</td>
</tr>
<tr>
<td>1 nasal stuffiness or unusually moist eyes</td>
<td>completing Assessment:</td>
</tr>
<tr>
<td>2 nose running or tearing</td>
<td></td>
</tr>
<tr>
<td>4 nose constantly running or tears streaming down cheeks</td>
<td></td>
</tr>
</tbody>
</table>

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

From: Wesson DR, Ling W J Psychoactive Drugs 2003 Apr-June; 35(2): 253-9
Buprenorphine Initiation

- First dose; 2-4mg
- Reassess after at 1.5-2 hours
- If needed, additional dose can be given on day 1

- Precipitated withdrawal;
  - Withdrawal symptoms worsen dramatically within an hour of first dose
  - Non-opioid symptomatic treatment (eg. clonidine, NSAIDs, antiemetic, etc.)
  - Try again tomorrow
Precipitated Withdrawal

- A result of buprenorphine’s high receptor affinity but lower intrinsic opioid activity
- Reduction in opioid activity can be felt as opioid withdrawal
- Will occur if buprenorphine is given to an opioid dependent patient, while affected by another opioid
**Precipitated Withdrawal**

**Intoxication**
Significant amount of opioid bound to receptors
*“Volume” on max*

**Buprenorphine**
Binds preferentially to receptors
*“Volume” on medium*

*Precipitated Withdrawal:*
Relative to intoxication, Buprenorphine “turns on” receptors less so patients feel withdrawal

Graphics adapted from NAABT, Inc. (naabt.org)
Precipitated Withdrawal

**Withdrawal**
Most receptors unbound

“Volume” on *low*

**Buprenorphine**
Binds preferentially to receptors

“Volume” on *medium*

**Induction:**
relative to withdrawal, Buprenorphine “turns on” receptors more so patients feel better.

Graphics adapted from NAABT, Inc. (naabt.org)
Protocol for Use of Buprenorphine in the ED

Toronto, Ontario

- St. Joseph’s Health Centre
- Dr. Meldon Kahan and the Addiction Medicine Service
- Protocol currently being implemented at 7 hospitals across Ontario
<table>
<thead>
<tr>
<th>PHYSICIAN ASSESSMENT (physician to complete)</th>
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<tbody>
<tr>
<td>☑ Opioid used: __________  Time of last Opioid intake: ____ : ____ (24h)</td>
</tr>
<tr>
<td>☑ Clinical Opiate Withdrawal Scale (COWS) q 2H</td>
</tr>
<tr>
<td>Buprenorphine 2-4 mg SL for COWS score 12+ AND:</td>
</tr>
<tr>
<td>- 12+ H since last opioid dose OR 72+ H since last methadone dose</td>
</tr>
<tr>
<td>☑ MAXIMUM 10 mg Buprenorphine / 24 hours on first day</td>
</tr>
<tr>
<td>Hold if drowsy</td>
</tr>
<tr>
<td>DC COWS if &lt; 5 on 2 consecutive occasions</td>
</tr>
<tr>
<td>☑ Dimenhydrinate 50mg PO/V/IM Q4H PRN</td>
</tr>
<tr>
<td>☑ Loperamide 4 mg PO PRN then 2 mg PO PRN with each BM – max 16mg/24 hours</td>
</tr>
<tr>
<td>☑ Acetaminophen 650 mg PO Q4H PRN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DATE</th>
<th>TIME (24h)</th>
<th>SIGNATURE</th>
<th>PRINT NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0 / MM / YYYY</td>
<td></td>
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Protocol for the Use of Buprenorphine in Acute Care

Edmonton, Alberta

- Royal Alexandra Hospital
- Addiction Recovery and Community Health Team (ARCH)
ARCH Protocol - Flexible with COWS

- COWS score q2-4h
- Buprenorphine 2mg sl for COWS >12
  - Buprenorphine 4mg sl for COWS >24
  - AND 12+ hours since last opioid use or 72+ hours since last methadone use
- D/C COWS if <5 on two consecutive occasions
- Maximum buprenorphine 10mg/24 hours on first day
  - Maximum buprenorphine 16mg/24 hours on second day
  - Hold if drowsy
- Maintain second day dose on day three, split dose bid
- Taper over remainder of admission, no more than 2mg per day
ARCH Protocol - Flexible without COWS

- Day one: Buprenorphine 2mg sl q4h prn “opioid withdrawal” AND 12+ hours since last opioid use or 72+ hours since last methadone use
  - Maximum buprenorphine 10mg/24 hours
  - Hold if drowsy
- Day two: Buprenorphine 2mg sl q4h prn “opioid withdrawal”
  - Maximum buprenorphine 16mg/24 hours
  - Hold if drowsy
- Maintain second day dose on day three, split dose bid
- Taper over remainder of admission, no more than 2mg per day
Key Points about Opioid Detoxification

- Relapse after detoxification is extremely common
- Due to the loss of tolerance to opioids, the most dangerous time to relapse is after a period of non-use
- Detoxification on its own is not considered treatment for a substance use disorder
Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

Gail D’Onofrio, MD, MS; Patrick G. O’Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD

[+] Author Affiliations


OBJECTIVE To test the efficacy of 3 interventions for opioid dependence:
1. Screening and referral to treatment
2. Screening, brief intervention, and facilitated referral to community-based treatment services
3. Screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care
RESULTS

- Engaged in addiction treatment on the 30th day after randomization
  - Buprenorphine group - 78%
  - Brief intervention group - 45%
  - Referral group - 37%
- Reduced number of reported days of illicit opioid use per week
  - Buprenorphine group - 5.4 to 0.9 days
  - Brief intervention group - 5.6 to 2.4 days
  - Referral group - 5.4 to 2.3 days
- Use of inpatient addiction treatment services
  - Buprenorphine group - 11%
  - Brief intervention group - 35%
  - Referral group - 37%
- No difference in rates of urine samples that tested positive of opioids or of HIV risk
Clinical Case

46 year old man, presenting to the ED requesting help for opioid withdrawal

- 4 year history of IV opioid use, currently using morphine 200-300mg daily
- Remote history of severe alcohol use disorder and cocaine use, after long-term residential treatment he was able to achieve several years of abstinence
- After a back injury, he started using prescription opioids (initially prescribed then illicit)
- Unemployed and on social assistance, living in a motel
- Last use was about 16 hours ago, he is wanting help to come off the morphine
Clinical Case

- On entering the ED, he was in mild opioid withdrawal
- On assessment, he is now in severe opioid withdrawal - restless, diaphoretic, vomiting, and unable to participate well in assessment/treatment planning
  COWS score - 26
- EKG and urine drug screen ordered
- Buprenorphine 4mg ordered

- Phone call made to local Opioid Dependency Program about next admission date
Clinical Case

- Reassessed 60 minutes after dose - Sleeping peacefully

- Reassessed 30 minutes later - Now awake, sitting in bed appearing comfortable, mild subjective symptoms reported only (ED physician “He’s eating a sandwich!!”)
  - Able to discuss treatment planning, agreeable to follow up at opioid dependency clinic in 2 days
  - Given second dose of buprenorphine 4mg shortly afterwards and discharged home
Clinical Case

- Phone call with patient the next day
  - Still feeling well, buprenorphine 8mg total dose lasted 24 hours
  - Prescription faxed to pharmacy for another dose of buprenorphine 8mg

- Followed up with opioid dependency program on day 3 and continued initiation/stabilization on buprenorphine
Next Steps?

- Further study and evaluation of protocols to treat opioid withdrawal with buprenorphine in the ED and to initiate buprenorphine in the ED
- Advocacy to improve access to buprenorphine and relax restrictions in place on prescribing
- Further training in buprenorphine prescribing:
  - [www.suboxonecme.ca](http://www.suboxonecme.ca)
  - Ontario: CAMH Opioid Dependence Treatment Core Course ([www.camh.ca](http://www.camh.ca)), also used in Nova Scotia
Questions?

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@TeamARCH