Buprenorphine – when is it advised over Methadone?

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FACULTY/PRESENTER DISCLOSURE

• Faculty: Dale Wiebe

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MITIGATING POTENTIAL BIAS

- No financial interest in True North Medical Centre
Objectives

• List the benefits and review pharmacology of buprenorphine/naloxone

• Cite the CAMH practice guideline (CPG) for the use of buprenorphine/naloxone and discuss

• Review factors favouring use of buprenorphine/naloxone over methadone
  – Efficacy, safety and adverse effects
Methadone
Buprenorphine
Buprenorphine Treatment Setting

• *Buprenorphine/naloxone maintenance treatment can be prescribed to patients in either a primary care setting or in a specialized addiction treatment setting.* [I, A].

• Intro p.12: “Advisable for a physician or pharmacist with no experience in opioid maintenance treatment to complete a formal program (examples: Appendix I)
Prescriber Qualifications

- Product monograph:
  - Prescribers should meet the following requirements:
    - “experience in substitution treatment in opioid drug dependence”
    - “completion of a recognized SUBOXONE® Education Program”

- CPSO:
  - Buprenorphine prescribing course
  - Observe
Product Monograph Changes

• Product monograph June 2013:
  – “substitution treatment in opioid drug dependence in adults”

• Product monograph August 2015:
  – “substitution treatment in adults with problematic opioid drug dependence”
  – Cautious dose selection for elderly (>65)
    • More decreased hepatic, renal, respiratory or cardiac function, concomitant disease, other drug therapy
  – Children <18
    • safety and efficacy not established
    • not recommended
    • FDA in USA recommends 16 or older and Ontario age of consent is 16 years old
  – No carry restriction in first month – clinical decision
Buprenorphine in Primary Care

- France’s buprenorphine maintenance has largely been prescribed by primary care physicians

  - Buprenorphine 80%, methadone 20%
  - OD deaths decreased 79%

- Buprenorphine as effective and safe in primary care compared to specialty clinics
  - Gibson et al. Med J Australia 2003;179:38-4
Buprenorphine Pharmacology
(Gowing et al. 2006)

• High affinity for mu opioid receptor
  • binds tightly
  • blocking the effect of other opioids
• Partial agonist
  • Less risk of overdose and respiratory depression
• Long half-life
  • allows less-than-daily dispensing
  • possibly easier withdrawal
Buprenorphine Pharmacology

- **Mu receptor partial agonist**
  - Ceiling effect for opioid agonist properties
    - Walsh SL et al. 1994

- **Kappa receptor antagonist**
  - Offsets the respiratory depression effect at higher doses?
  - Decreased dysphoria observed in some studies
    - Johnson et al. 2003

### Opioid Effect

<table>
<thead>
<tr>
<th>Dose of Opioid</th>
<th>Fatal Respiratory Depression</th>
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<tr>
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<td>Full Agonist e.g. morphine Partial Agonist</td>
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### Opioid Effect Diagram

- **Mu receptor** – analgesia, respiratory depression, pupillary constriction, ↓bowel mobility, sedation
- **Kappa receptor** – analgesia, dysphoria, diuresis, ?addiction
BMT – Induction: Precipitated Withdrawal

**Intoxication**
- Significant amount of opioid bound to receptors
- "Volume" on max

**Buprenorphine**
- Binds preferentially to receptors
- "Volume" on medium

**Withdrawal**
- Most receptors unbound
- "Volume" on low

**Buprenorphine**
- Binds preferentially to receptors
- "Volume" on medium

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**Precipitated Withdrawal**
- Relative to intoxication, **Suboxone®** “turns on” receptors less
- Patient feels withdrawal

**Induction**
- Relative to withdrawal, **Suboxone®** “turns on” receptors more
- Patient feels better
Available in Canada as sublingual tablet
  Takes a few minutes to dissolve
  Film may be coming soon

Rapid absorption by buccal mucosa

Slow release into bloodstream
  45 min – 1.5 hours

Peak plasma concentration in 1 – 4 hours

Very low oral bioavailability due to first pass effect

Can be abused intravenously (reason for naloxone) or intra-nasally
Opioid Agonist Treatment (OAT)

- Observational studies demonstrate reduced mortality for individuals on OAT compared to those off OAT.
  - Gronbladh L et. al., 1990
  - Caplehorn JRM et al., 1994

- Reduced risky behaviour and decreased HIV seroconversion rates
  - Gowing et. al., 2008
  - Metzger et al., 1993
Efficacy: Buprenorphine vs. Methadone
(Mattick et al. 2014)

- Methadone and Buprenorphine both superior to placebo
  - retention in treatment
  - reduced illicit opioid use
- Flex dose methadone appears marginally better in terms of treatment retention (RR 0.83, 0.72-0.95).
- Equivalent with respect to reducing illicit opioid use
- ? Old evidence generalizable to oral prescription opioid (PO) dependent patients
Efficacy: Buprenorphine vs. Methadone

(Mattick et al. 2014)

- Quality of buprenorphine induction
  - Too slow?
    - Advantage of buprenorphine is faster titration
  - Precipitated withdrawal?
- Partial vs. full \( \mu \) agonist differences?
  - Maximum tolerance level for buprenorphine?
- More tolerable buprenorphine withdrawal reducing treatment retention?
- Fixed dosing not real life-practice
  - Difficult to compare flex dosing with two medications
BMT: Prescription Opioids (PO)

(Moore et al. 2007)

• PO evidence remains scant
  • No MMT vs BMT studies
• PO users more likely compared to heroin users:
  • White
  • Younger
  • Earn more income
  • Fewer years of opioid use
  • Less drug treatment history
  • Less likely to have Hep C
• Outcomes for PO vs. heroin users
  • Better retention (59 vs 30%)
  • Reduced opioid use (56 vs 40%)
BMT: Prescription Opioids (PO)
(Parran et al. 2010)

- Long term BMT
- 18 - 42 month follow-up
- Both low and high SES populations
- More likely to promote:
  - Self-help group attendance
  - Employment and occupational stability
  - Improved psychosocial outcomes
BMT: Prescription Opioids (PO) (Nielsen 2015)

- RCT with BMT & behavioural treatment for 16 weeks
  - Prescription opioid (PO) - 54
  - Prescription opioid and heroin (POH) - 71
  - Heroin (H) - 54
- PO group provided more opioid-negative UDS
  - Over the combined treatment period
    - PO: 70%, POH: 40%, H: 38% (p<0.001)
    - End of the combined treatment period:
      - PO: 65%, POH: 31%, H: 33% (p<0.001)
- Retention highest in PO group, lowest in H group
  - PO: 80%, POH: 65%, H: 57% (p=0.039)
BMT vs. MMT: Prescription Opioids (PO)

• Remember Cochrane review (Mattick et al. 2014):
  – Treatment retention marginally better with MMT than BMT
  – Reducing illicit opioid use – MMT and BMT equivalent

• But... do MMT and BMT have similar differential between oral PO versus heroin use:
  – Treatment retention?
  – Reduced illicit opioid use?

• Could BMT produce higher retention rates and reduce illicit opioid use more than MMT?
Safety: Buprenorphine vs. Methadone

- French population-level data 1994-1998
  - 3x less mortality due to buprenorphine than due to methadone
  - “46 rather than 288 deaths” (Auriacombe 2001)
- Post-mortem studies:
  - lower rate of overdose deaths involving buprenorphine compared to methadone (Pirnay 2004, Soyka 2006, Gibson 2007)
    - “underestimate of buprenorphine deaths”
- More OD symptoms with methadone than buprenorphine (Nielson 2007 and 2008)
- Higher hospitalization rates, greater ICU utilization rates, and considerably worse medical outcomes with nonmedical methadone vs. buprenorphine. (Lee 2013)
Safety: Buprenorphine vs. Methadone

- Buprenorphine implicated in some OD deaths
  - Almost exclusively (116/117) in combo with other sedating substances (Kintz 2001)
  - 7/43 buprenorphine-alone deaths in UK 1980-2002 (Schifano 2005)
- No difference in mortality between methadone and buprenorphine (Ling 1996, Gibson 2008, Soyka & Apelt 2006)
- Buprenorphine more non-fatal heroin OD’s than methadone (P=0.08) (DiGiusto 2004)
- Buprenorphine safer in combination with ARV’s (Gruber 2010)
Safety: Buprenorphine/Naloxone Injection

• Plenty of evidence that buprenorphine monoprodct is injected (Obadia 2001, Vidal-Trecan 2003)

• Much more than methadone (Barrau 2001)

• Evidence that bup/nlx is pleasurable to non-dependent users (Strain 2000, Weinhold 1992)

• IV Bup/nlx pleasurable in bup/nlx maintained subjects (Bell 2007)

• Case reports of hepatotoxicity if abused IV (Herve 2004)
Safety: Buprenorphine/Naloxone Injection

- Naloxone was introduced to deter IV use

- Naloxone:
  - opioid receptor antagonist
  - binds opioid receptor, but no intrinsic activity
  - precipitates withdrawal if physically dependent on opioids (how long?)
  - little to no sublingual or oral bioavailability
  - deterrent only when used IV
Safety: Buprenorphine/Naloxone Injection

- *But naloxone...*

- Only partially blocks opioid receptor binding

- Has much shorter duration of action than buprenorphine

- Combo product is abused despite “deterrent effect”

Fig. 3. A semilogarithmic plot of the time course of mean plasma levels of buprenorphine and naloxone following an intravenous administration of a combination of 4 mg buprenorphine and 4 mg naloxone in nine subjects (data from Jones and Upton, 1997).
Safety: Benzodiazepine risk
(Lee SC et al. 2014)

• “Nonmedical use of benzodiazepines with methadone is associated with higher rates of hospitalization, greater ICU utilization rates and considerably worse medical outcomes when compared to nonmedical use of benzodiazepines with buprenorphine.”
Safety: Benzodiazepine risk
(Lee SC et al. 2014)

- Clinical effects in methadone-BZD and BUP-BZD groups:
  - lethargy (71.1%, 59.7%)
  - respiratory depression (29.0%, 15.3%)
  - coma (22.4%, 5.6%)
  - respiratory arrest (4.5%, 0)
  - hypotension (11.8%, 2.8%)
  - cardiac arrest (1.9%, 0)
- Methadone-BZD group four-times more likely than in the BUP-BZD group to:
  - receive naloxone (60.4% vs 15.3%)
  - be intubated (16.3% vs 4.2%)
- Hospitalization rates highest for methadone-BZD patients (67.3%) vs. BUP-BZD patients (43.3%)
Safety: Buprenorphine vs. Methadone

• CPG Recommendation 10

• Policy makers should be aware that in countries where buprenorphine is equally available as methadone, buprenorphine has a lower attributable death rate than methadone. [II-3, A]
OAT: Buprenorphine vs. Methadone

- CPG Recommendation 4

- The decision to initiate opioid agonist therapy with either buprenorphine/naloxone or methadone maintenance should be guided by the individual clinical circumstances and the patient’s preferences. [III, I]
OAT: Buprenorphine vs. Methadone

• CPG Recommendation 12

• Buprenorphine/Naloxone may be preferred over methadone if...
  • Absolute contraindication:
    • QT prolongation risks (Level I, Grade A)
    • Allergy to methadone (Level III, Grade A)
  • Adverse effects:
    • Sexual side effects (Level II-2, Grade B)
    • Severe sedation or constipation on methadone (Level III, Grade C)
OAT: Buprenorphine vs. Methadone

- CPG Recommendation 12 (continued)

- *Buprenorphine/Naloxone may be preferred over methadone if...*
  - Increased risk of opioid toxicity from full *mu* agonist:
    - Lower opioid tolerance suspected (Level III, Grade B)
    - Heavy or unstable use of sedating medication/drugs (Grade II-3, Grade B)
    - Elderly (Level III, Grade B)
    - Significant Respiratory illness (Level III, Grade B)
OAT: Buprenorphine vs. Methadone

• CPG Recommendation 12 (continued)

• *Buprenorphine/Naloxone may be preferred over methadone if...*
  • Good prognostic factors
    • Age – adolescents and young adults (Level III Grade B)
    • Brief opioid use history, < 1 year (Level III, Grade C)
    • Social supports (Level III, Grade C)
  • Past successful stabilization with buprenorphine (Level III, Grade I)
  • Methadone less accessible (clinic or pharmacy) or unavailable in timely manner (level III, Grade B)
OAT: Buprenorphine vs. Methadone

- CPG Recommendation 13

- *Methadone may be preferred over buprenorphine/naloxone*
  - Allergy to buprenorphine (Level III, Grade A)
  - Pregnancy (naloxone), can use buprenorphine monoprodut (Level III, Grade A)
  - Induction withdrawal dangerous (cardiovascular instability) (Level III, Grade B)
  - History of injecting buprenorphine/naloxone (Level III, Grade A)
  - Previous inability to stabilize on buprenorphine (Level III, Grade B)
  - Previous success with methadone (Level III, Grade I)
  - Severe dry mouth interfering with SL absorption (Level III, Grade A)
  - Patient choice – ability to pay (Level III, Grade B)
Buprenorphine Payment

• Buprenorphine/naloxone is covered for Limited Use in Ontario:
  – LU code 437:
    • Failed methadone
    • Intolerance
    • Contraindication (ie QT, allergy)
    • Higher risk for opioid toxicity
      – BZ, alcohol, p450 inhibitors, elderly, lower tolerance
  – LU code 438:
    • MMT program is not available or accessible > 3 months
• Observed vs. take home dose cost
  – Increased incentive to obtain take home doses
BMT vs. MMT: Take-Home Doses

• CPG Recommendation 9

• In making decisions regarding the provision of take-home doses of buprenorphine/naloxone, providers should use a clinical risk stratification strategy (as described in the clinical considerations) that aims to support patient autonomy while at the same time respecting patient and public safety. [III, A]
BMT vs. MMT: Take-Home Doses

- Health Canada & Product Monograph:
  - 2013: daily observed for 2 months, except weekends and holidays (if pharmacy closed)
    - Followed MMT Guidelines but no evidence supporting this
  - 2015: take-home doses once the patient has sufficient clinical stability and is able to safely store SUBOXONE®
    - Assess and review take-home doses on a regular basis.
BMT vs. MMT: Take-Home Doses

- When deciding about take-home doses
  - Is it safe for the patient?
  - Is it safe for the public?
  - What is the risk of diversion?

- Early in treatment: 3 categories
  - Too unstable for any take-homes, including weekends and holidays
  - Appropriate for “weekend and holiday” take-homes
  - Appropriate for accelerated take-home doses beyond “weekends and holidays” within the first 2 months
1. Too Unstable for Take-Home Doses

- Recent IV drug use
- Recent suicidal ideation
- Significant cognitive impairment
- Unstable housing
- Ongoing opioid use
- Other active alcohol or drug dependencies
- “Concern NYD”
2. Weekend & Holiday Take-Home Doses

- No recent IV drug use
- No recent suicidality
- No significant cognitive impairment
- Stable housing
- Abstinent from opioids
- No other active alcohol or drug dependencies
- No “concern NYD”
3. Accelerated Take-Home Doses

- Clinical stability beyond category 2:
  - No significant psychiatric co-morbidity
  - Particularly stable social situation
- Overly restrictive take-home dosing may lead to treatment drop out
  - Pharmacy access limited
    - Employment conflicts
    - Distance
    - Poor transportation access
  - Cost of frequent dispensing
  - Other limitations?
Accelerated Take-Home Doses

- If providing accelerated take-homes:
  - Consider other options first
    - EOD dosing
    - pharmacy change
  - Discuss risks of “accelerated” take-homes
    - Is it safe for the patient?
    - Is it safe for the public?
    - What is the risk of diversion?
  - Monitor closely to ensure benefit
  - Document carefully
Contingency Management

• Increase number of weekly take-home doses gradually based on clinical progress
• Suggested maximum of 6 – 13 consecutive take-home doses
  • Dispensed weekly to biweekly
  • Dispensed between witnessed doses
• If relapse to problematic drug use or compromised clinical stability:
  • Increase visit frequency (weekly)
  • Increase UDS frequency
  • Increased number of witnessed doses (decrease take-home doses)
BMT vs. MMT: Adverse Effects

• Common patient complaints with methadone:
  – Cognitive function (“mental fog”)
  – Mood symptoms
  – Constipation
  – Sweating
  – Weight gain - no conclusive evidence (MMT)
  – Nausea
  – Sexual side-effects
  – Bone density (“rots your bones”)
  – Dental health (“rots your teeth”)
  – Methadone handcuffs – ease of taper

• Less stigma with buprenorphine but less complaints?
BMT vs. MMT: Cognitive Function

(Rapeli et al. 2008)

• “non-randomized clinical studies buprenorphine patients tend to perform better than methadone patients.”

• “A longitudinal study of opioid substitution treated patients who switch from buprenorphine to methadone or vice versa would be ideal in detecting cognitive effects of these drugs and the roles of other clinical variables.”

• Anecdotal effect with improved cognitive function after transition from MMT to BMT
  – Needs more study
Concurrent Depressive Symptoms
(Gerra et al 2004, 2006; Ehrich 2015)

• “[Buprenorphine] seems to be more effective than [Methadone] in patients affected by depressive traits and dysphoria, probably due to antagonist action on κ-opioid receptors.”

• Anecdotal mood and anxiety symptom improvement with MMT to BMT transition at CAMH

• Combination buprenorphine + samidorphan (mu opioid antagonist) showed antidepressant activity for MDD (Ehrich 2015)

• kappa opioid antagonism?
  – Need more study of opioid modulation
Subjective reports of both constipation and sweating worse with methadone
BMT vs. MMT: Sexual Dysfunction
(Yee 2014)

• “Evidence showed that the prevalence of sexual dysfunction was higher among the users of methadone compared with buprenorphine. Patients with sexual difficulty while on methadone treatment were advised to switch to buprenorphine.”

• meta-analysis of 1,570 participants, 16 studies

• sexual dysfunction among methadone users with a meta-analytical pooled prevalence of 52% (95% confidence interval [CI], 0.39-0.65)

• significantly higher combined odds ratio in the methadone group (OR = 4.01, 95% CI, 1.52-10.55, P = 0.0049)
BMT vs. MMT: Bone Density

(Grey 2011)

• BMD is lower than normal throughout the skeleton in men, but not women, taking MMT.

• Assessment of skeletal health, including estimation of absolute fracture risk, should be undertaken in men participating in methadone maintenance programmes.

• Increased risk with HIV infection
BMT vs. MMT: Oral Health

- Methadone detrimental to oral health (Brondani 2011)
- Case series of declining oral health on buprenorphine (Suzuki 2012)
  - But a majority of patients reported:
    - Cigarette smoking
    - Bruxism
    - Regular soda consumption
    - Moderate dental hygiene practices
    - Use of other psychotropic medications
    - All factors known to negatively impact oral health.
Buprenorphine taper

(Nielsen 2013)

• Short term taper is not recommended as a stand-alone treatment but...

• Patients may taper from buprenorphine as part of a treatment plan but maintenance yields better abstinence (Fiellin 2014)

• Despite greater co-morbidity, PO users have favorable taper outcomes compared to heroin users (Nielsen 2013)

• Longer tapers 4 > 2 > 1 week more associated with prolonged abstinence (Sigmon 2013, Katz 2009)
  – Except one study found no advantage to prolonging the taper (Ling 2009)
Summary: Buprenorphine vs. Methadone

• Differentiating Factors guiding medication choice
  – Effectiveness – insufficient study of BMT vs. MMT for oral PO
    • Treatment Retention
    • Reduced illicit opioid use
  – Safety profile
    • OAT patient safety (OD risk, misuse of take home doses)
    • General public safety (diversion)
  – IV opioid versus oral PO use
Summary: Buprenorpinhine vs. Methadone

• Differentiating Factors guiding medication choice
  – Adverse effects
  – Concurrent substance use
  – Concurrent disorders
    • Medication interaction
    • Medication compliance
  – Patient specific factors:
    • Adult versus adolescent
    • Pregnancy
  – Autonomy: patient preference
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