Optimizing Suboxone in Opioid Addicts

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K30 Translational Research Interest
March 24, 2009

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Overview

• Background on Opioid Addiction
• Negative Effects Associated with Opioids
• Opioid Neurophysiology
• Preliminary Study Results
• Future Directions
Background

- 810,000 to 1,000,000 chronic users of heroin

- 250,000±patients receiving opioid maintenance treatment—buprenorphine and methadone. (SAMHSA, TEDS)
Number of new non-medical users of therapeutics
“…Lull all pain and anger, and bring forgetfulness of every sorrow.”  Odyssey

“Among the remedies which it has pleased Almighty God to give to man to relieve his suffering, none is so universal and so efficacious as opium.”  Thomas Sydenham 1680

“It banishes melancholy, begets confidence, converts fear into boldness, makes the silent eloquent and bastards brave”  John Brown
Positive Effects of Opioids

- **Desirable:** Analgesia, Relief from anxiety

- **Possibly Desirable:** Sedation, Cough suppression, euphoria (increased “hedonic tone”)

Opium

Opiate—an unlocked door in the prison of identity. It leads into the jail yard.
- Ambrose Bierce, The Devil’s Dictionary

The junk merchant does not sell his product to the consumer, he sells the consumer to the product. He does not improve and simplify his merchandise, he degrades and simplifies the client.
- Burroughs
Negative Effects of Opioids

- Respiratory depression
- Nausea, vomiting
- Constipation
- Urinary retention
- Altered mental status
- Pruritis
- Ileus
- Biliary spasm
- STD transmission
- Tolerance, Abuse, and Dependence
Effects of Long-Term Opioid Use

Hormonal
--- Decreased plasma cortisol levels
--- Increased plasma prolactin levels
--- Decreased levels of LH, FSH, testosterone, estrogen

Hyperalgesia

Sleep Apnea
Effects of Long-Term Opioid Use

Immunosuppression

--Suppression of natural killer cell activity, inflammatory cytokine production, and mitogen-induced lymphocyte proliferation
The Opioid Receptor Family

- **Potentially lethal dose**
- **Positive effect**
  - Full agonist: morphine/heroin, hydromorphone
  - Partial agonist: buprenorphine
- **Negative effect**
  - Antagonist: naltrexone
  - Antagonist + agonist/partial agonist

### Schematic of MOR-1 Splice Variants

- MOR-1
- MOR-1A
- MOR-1B
- MOR-1C
- MOR-1D
- MOR-1E
- MOR-1F

### Opioids: Pain Modulation

- Peripheral nociceptor
- Presynaptic receptor
- Enkephalin interneurons
- Presynaptic receptors
- Supraspinally
- Descending systems

### Notes

- Full agonists: morphine, heroin, hydromorphone
- Partial agonists: buprenorphine
- Antagonists: naltrexone, antagonists + agonists/partial agonists
Opioid Pharmacogenomics

Splice variants on mu opioid receptor gene alters functional characteristics leading to functionally distinct receptor subtypes.

- This affects potency, efficacy, tolerance, crossed tolerance, and side effect profile.

More specifically: oral absorption, first pass metabolism, hepatic enzymes, CNS penetration, receptor binding, and dose limitation.
Buprenorphine for Opioid Dependence

- FDA approved 2002 (Schedule III), age 16+
- Mandatory certification from DEA (100 pt. limit)
- Mechanism: partial mu agonist
- Office-based, expands availability
- Analgesic properties
- Ceiling effect
- Lower abuse potential
- Safer in overdose

Suboxone Tablets 8mg. and 2mg
Buprenorphine: Pharmacological Characteristics

Partial Agonist (ceiling effect)
- less euphoria
- safer in overdose

Induction: stabilization period only 3 days

High Receptor Affinity
- long duration of action
- 1st dose given during withdrawal, because buprenorphine will displace other opioids

![Graphs showing pharmacological characteristics of buprenorphine]
**Optimizing Outcomes Using Suboxone® for Opiate Dependence**

*Opioid-dependent patients treated with buprenorphine must also be provided or referred to ancillary psychosocial treatment (Controlled Substances Act, FDA website 2002), although the interpretation of this requirement may vary greatly.

*No previous research has systematically examined the psychosocial treatment component associated with buprenorphine administration. It is unclear the role that psychosocial treatment plays in buprenorphine treatment success, and if treatment outcomes can be improved by specific psychosocial treatment types or components.
Primary Objective

To compare the effectiveness of four psychosocial treatment conditions in combination with pharmacotherapy with buprenorphine for the treatment of opioid dependence:

1. Cognitive-Behavioral Therapy (CBT), Contingency Management (CM), and Medical Management (MM)
2. CBT + MM
3. CM + MM
4. MM only
Study Design

• Phase 1: Screening, Baseline Assessment (Week 0)
• Phase 2: Induction & Stabilization onto Suboxone (Week 1-2); Randomized into 1 of 4 treatment groups (n=60 for each grp)
• Phase 3: Twice weekly clinic visits for combined MM & Behavioral Therapy, or only MM
Study Design

- Phase 4: Post-Behavioral Treatment Assessment (Week 18)
- Phase 5: Suboxone Only Treatment (Weeks 19-34)
- Phase 6: Suboxone Taper (Week 35-40)
- Phase 7: Week 40 Follow-Up Assessment
- Phase 8: Distal Follow-Up Assessment (Week 52)
Participants

*240 opioid-dependent males and non-pregnant females (at least 15 years of age), stabilized for two weeks on buprenorphine

*Inclusion Criteria:
• Meet DSM-IV-TR criteria for opioid dependence.
• Be in good general health or, in case of a medical/psychiatric condition needing ongoing treatment, be under the care of a physician who provides documented willingness to continue participant’s medical management and coordinate care with the study physicians.
• If female and of child bearing potential, agree to use birth control
Participants

- **Exclusion Criteria:**

  - Be dependent on alcohol, benzodiazepines or other drugs of abuse that require immediate medical attention.
  - Have a medical or psychiatric condition that would, in the opinion of the study physician, make participation medically hazardous
  - Have a current pattern of benzodiazepine use, as assessed by the study physician, which would preclude safe participation in the study.
  - Be a nursing or pregnant female.
  - Be a female of childbearing potential who does not agree to use a medically acceptable method of birth control
  - Have any pending legal action that could prohibit continued participation for the one-year period of study participation (such as that which could possibly result in incarceration).
  - Have been previously randomized to a treatment condition in this study.
Study Assessments

**Medical:**

*Medical History, Vital Signs & Physical Examination*
*Basic Laboratory Tests (blood chemistry, hematology, medical urinalysis)*
*Prior/Concomitant Medications*
*Hepatitis Panel*
*Pregnancy Test*
*12-lead EKG Test*
Study Assessments

**Psychological:**

* Ancillary Psychosocial Treatment
* Addiction Severity Index
* Attitudes & Beliefs
* Beck Depression Inventory
* DSM-IV Checklist for Opioid Dependence
* Mini-International Neuropsychiatric Interview
Study Assessments

Drug Use, Craving and Withdrawal:

*Clinical Opiate Withdrawal Scale (subjective and objective)

*Substance Use Report

*Urine Drug Screen

*Visual Analog Scale to assess cravings
Planned Analyses

• **Primary Analyses**: Treatment Effectiveness Score (The number of opioid-free urine samples by treatment condition)

• **Secondary Analyses**:
  1. Pre- and post-treatment functioning
  2. Outcome by type of opioid used (i.e., prescription vs. heroin)
  3. Sustained effects of treatment
Preliminary Results

- We evaluated the first 43 participants during the psychosocial treatment phase (weeks 3-18) to determine whether there are differences in retention by psychosocial condition.
- Results indicate no differences between study conditions.
Preliminary Results

• The percentages of participants in each condition completing the 18-week psychosocial treatment phase are:

  CBT+MM = 81.8%
  CM+MM = 72.7%
  CBT+CM+MM = 77.8%
  MM only = 58.3%.
Future Directions

• Safety/efficacy studies: IV Buprenorphine vs. IV Full Opioid Agonists
• Implantable Buprenorphine vs. Implantable Opioid Antagonists
THANK YOU!