# Buprenorphine and Methadone in the Treatment of Pain

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# Objectives

- Review buprenorphine and methadone in the context of pain management
- Consider the evidence for their use in pain management
- Discuss clinical implications / opportunities /risks

# Brief Overview

- Buprenorphine is a semisynthetic partial μ agonist (and κ antagonist)
  - Initially used as analgesic; now 1º Maintenance Agonist Therapy (MAT)
  - Linear μ effect at lower doses
  - Morphine equivalency of ~40:1 over linear range
  - Improved safety profile due to "Ceiling Effect"
  - (Available as sl mono/naloxone-combo tablet and TDS-matrix buprenorphine)

# Pharmacology

- Derived from opium alkaloid Thebain
- Terminal Elimination $t_{1/2}$~24-60 hours

  but:
  - Analgesic Duration of Action is ~6-8 hrs
  - MAT Duration of Action is ~24 – 48 hrs
- Poor oral bioavailability but well absorbed by sublingual / parenteral route
- CYP 450 3A4 metabolism (like methadone)

# Pharmacology

- Very high receptor affinity
  - Once attached, remains until the receptor is recycled
  - Incomplete receptor occupancy needed to effect MAT action
  - Can precipitate withdrawal in full μ dependent users
    - But can always add μ agonist to pt on Buprenorphine

# Abuse Liability

- As the mono product, Buprenorphine is identified as an opioid by experienced users
  - In the opioid naïve user, μ effects dominate
  - In the opioid dependent user, withdrawal can occur (precipitated) especially if:
    - Recent (<2 hr) use of μ agent
    - Highly opioid dependent *not* in withdrawal
  - Matrix systems can have unique risks

# Abuse Liability

- As the comb. product, Bupe/Naloxone; naloxone effect is minimal via s/l routes but dominant via IV route
  - In the opioid naïve user, μ effects likely dominate
  - In the opioid dependent user, withdrawal can occur especially if:
    - Recent (<2 hr) use of μ agent
    - Highly opioid dependent
  - Appears to be "less likable" than mono

# Relapse

- Buprenorphine can be safely increased, even after missing several days UNLESS:
  - Use of opioids has led to physical μ-agonist dependency
    - Unlike methadone where dangerous loss of tolerance can occur after only a few days, Buprenorphine can be increased even with sporadic attendance (ie crack cocaine relapses)

# Detoxification

- Buprenorphine withdrawal is said to be:
  - "a mild flu like syndrome"
    - w/d is highly variable but usually less than full μ agonists
- When used as a detox method, no studies to show outcomes better than methadone taper or clonidine-assisted detox
- Can be useful as part of "exit strategy"

# Currently Availability

- In Canada/USA
  - Subutex® / Suboxone® on-label use for maintenance therapy
    - Off label use in Pain Practice in various settings
      - In multiple daily doses for primary pain
      - OD or BID dosing for "opioid stabilization" in w/d mediated pain
      - Pharmacologically assisted "exit strategy"
  - Transdermal Matrix Buprenorphine
    - Bu Trans® in Canada / Butrans® in USA 7 day patch

# Novel uses of Buprenorphine

- Buprenorphine for pain management
  - Potent analgesic
  - Typically q 6-8 hr duration of action for pain
  - When coupled with naloxone, there may be analgesic potentiation d/t ultra low dose of μ antagonist effect
    - ? involve receptor upregulation
  - Clearly "off label use" of the drug (SL) but exciting possibilities in well selected pts

# Novel uses of Buprenorphine

- Intractable depression
  - Opioids play permissive role in hedonic tone
    - At least 1 paper describing use of buprenorphine in low dose as adjunct in treatment of intractable depression
  - We have several pts on SL buprenorphine whose depression now seems to be more responsive to Ψ pharmacotherapy
    - Endpoint is NOT mood improvement –partial agonist is used to*'normalize'* dysregulated endogenous μ system

# Methadone History

- Methadone as an Analgesic
  - Germany: Clinical trials 1st in 1942 (Amidone)
    - Undesirable side effects; not used during war
  - Became known as 'Methadone' in 1947
    - "Adolphine" coined in US in early 1970's
- Methadone for Opioid Addiction
  - 1963, Dr Robert Halliday, Narcotic Addiction Foundation of British Columbia 1st MMT program in Canada
    - 1965, Dole and Nyswander started Methadone Program in New York

# Methadone: The versatile drug

- Methadone is a great drug for:
  - Eliminating opioid withdrawal
  - Reducing opioid drug cravings
  - Blocking undesirable effects of other opioids
- But also:
  - Effective analgesic, especially in neuropathic pain
  - Reduces tolerance to other opioids
  - Stabilizes opioid levels

# Methadone for Analgesia

- Methadone exists as a racemic mixture of R- (R-Met) and S- (S-Met) configurations
  - μ activity resides solely with R-Met
  - NMDA antagonist activity with S-Met
  - Highly variable intra and inter patient dose equivalency
- Analgesic duration of action is 6-8hr in most situations

# Methadone for Analgesia

- Elimination half-life is highly variable
  - Typically 14-40h but >100h reported
  - Metabolized via CYP450 (3A4, 2B6)
  - pH dependent excretion fecal>urinary <55mg/d and pH < 6; EDDP no pH effect

# Methadone the "Unpredictable Drug"

- Methadone kills one of 3 ways:
  - Single overdose
    - i.e. accidental ingestion; over estimation of tolerance
  - Accumulated toxicity
    - i.e. too rapid induction
  - Drug-drug interactions
    - i.e. addition or subtraction of certain drugs

# Drug Interactions

- Addition of sedative class of drug
  - "Effect is greater than the sum of the parts"
    - Acute alcohol/benzodiazepine intoxication
- CYP450 active drug effect
  - Addition of *inhibitor* or discontinuation of *inducer* can lead to drug accumulation
    - Less of an issue with initial titration to effect
    - Potential for inhibition or induction isn't always clinically relevant

# Current Evidence

- Gordon, A et al Clin Ther. 2010 May; 32(5):844-60 Buprenorphine Transdermal System in Adults with Chronic Low Back Pain: A Randomized , Double-blinded, Placebo Controlled Crossover Study, Followed by an Open-label Extension Phase
  - 78 patients, Significantly better during TDS-Buprenorphine compared to placebo
  - No treatment differences in Pain Disability Index or Quebec Back Pain Disability Scale
- Gordon, A et al Pain Res Management 2010 May-June;15(3):169-78 Buprenorphine transdermal System for opioid therapy in patients with chronic low back pain– Randomized, double blinded, crossover study
  - 53 patients, improvements in mean daily pain scores vs placebo
  - Improvements in Pain Disability Index, Pain and Sleep(VAS), Quebec Back pain Disability Scale and Short-form 36 health Survey for both groups, without significant differences between treatments

# Current Evidence

- Goebel, A et al Eur J Pain. 2008 Apr;12(3):266-74 Buprenorphine injection to the stellate ganglion in the treatment of upper body chronic pain
  - 18 patients which failed to show superiority of GLOA (Ganglionide Local Opioid Application) over SSB (saline stellate ganglion block plus IM buprenorphine)
  - Procedure done in some European centers – not aware of use in North America
- Muriel, C et al Clin Ther. 2005 Apr;27(4):451-62 Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain
  - Multicenter, open label, uncontrolled prospective, observational clinical study
  - 1223 patients
  - Effective in alleviating cancer and non-cancer pain with good tolerability
  - Pts reported very good or good pain relief ($P<0.001$) from 3.6% baseline to 63.2% after 1 month, 56.85 after 3 months with improved Quality of Life (EQ-5D) from mean of 40.6 to 56.8 at 3/12

# Current Evidence

- Malinoff, HL et al. Am J Ther. 2005 Sep-Oct;12(5):379-84 Sublingual Buprenorphine is Effective in the Treatment of Chronic Pain
  - 95 patients, Single-center, open label study
  - 86% of patients experienced moderate to substantial relief of pain accompanied by both improved mood and functioning
- Sorge J, Sittl R Clin Ther. 2004 Nov;26(11);1808-20 Transdermal Buprenorphine in the Treatment of Chronic Pain: Results of a Phase III, Multicenter, Randomized, Double Blind Placebo controlled study
  - 18 patients who assessed pain intensity and pain relief better with TDS-Buprenorphine vs placebo but not statistically significant
- Morley, JS et al Paliat Med. 2003 Oct;17(7):576-87 Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind, randomized controlled crossover trial
  - 18 pts – compared to palcebo, 10mg BID resulted in stat significant improvements in VAS, Maximum pain intensity, average intensity and pain relief

# Current Evidence Methadone

- Mercadante, S et al Eur J Pain 2008 Nov;12(8):1040-6 Epub March 18. Sustained-release oral morphine vs transdermal fentanyl and oral methadone in cancer pain management
  - 108 pts, Multicenter, prospective, randomized controlled study did not show differences in pain and symptom intensity between treatments. Opioid escalation index was significantly lower in methadone patients ($P<0.0001$) but required up/down changes in dose
    - All three opioids used as first line therapy were effective, well tolerated and required similar amounts of co-medications. Methadone was significantly cheaper but required significant dose adjustment suggesting major clinical expertise

# Clinical Questions/observations

- In the case of TDS-buprenorphine, was success due to μ analgesic effect or, intrinsic stability of this agent in reversing withdrawal mediated pain and/or opioid induced allodynia?
  - Patients who seemed to benefit most were those who relied heavily on short acting IR agents eg Percocet®/Tylenol #3®

# Clinical Observations

- When clinicians implement opioid rotations
  - There is an opportunity to redefine boundaries and limits
  - There is also a potential missed opportunity to examine the role of the opioid class of drugs
    - μ analgesia or pseudo maintenance ie stabilizing withdrawal-mediated pain
    - If opioid responsiveness is unlikely, apparent success with new agent may be due to novelty or something other than μ analgesia

# Clinical Observations

- Buprenorphine products have a logical limit built into the molecule
  - This may make the tendency to ramp up the dose less likely than with full agonists
  - "No ceiling means no limit"
    - Perversion of a pharmacologic principle
  - Total daily dose of buprenorphine

# Conclusions

- Mounting evidence indicates that buprenorphine may be an effective analgesic agent with a better safety profile than traditional full μ agonists
  - However cost compared to methadone may limit use
  - When using TDS-buprenorphine or SL delivery, important to exploit all opportunities of this versatile molecule

# References


- Heit HA, Gourlay DL, Buprenorphine: New tricks for an old molecule. Clin J Pain 2008; 24:93-97
- Johnson RE, Fudala PJ and Payne, R, Buprenorphine: Considerations for Pain Management J of Pain and Symptom Management  2005; 29(3) pp297- 326


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