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 $\mu$ agonist (and $\kappa$ antagonist)
  – Initially used as analgesic; now 1º Maintenance Agonist Therapy (MAT)
  – Linear $\mu$ effect at lower doses
  – Morphine equivalency of $\sim$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 $t_{1/2} \sim 24$-60 hours but:
  – Analgesic Duration of Action is $\sim 6$-8 hrs
  – MAT Duration of Action is $\sim 24$ – 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 $\mu$ dependent users
    • But can always add $\mu$ 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, \( \mu \) effects likely dominate
  – In the opioid dependent user, withdrawal can occur especially if:
    • Recent (<2 hr) use of \( \mu \) 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 $\mu$-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 \( \mu \) 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 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 \textit{inhibitor} or discontinuation of \textit{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

  - 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

  – 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

  – 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

  - 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

  - 18 pts - compared to placebo, 10mg BID resulted in stat significant improvements in VAS, Maximum pain intensity, average intensity and pain relief
Current Evidence Methadone

  - 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 \( \mu \) 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

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