Buprenorphine/Naloxone for Opioid Dependence and the VA-WRJ Experience

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Outline

• Buprenorphine/Naloxone
  – Drug properties
  – Dosing
  – Duration
  – Discharges

• VAMC experience

• Challenges
  – Cannabis, alcohol
  – Diversion
  – Pain management
How Does Buprenorphine Work?

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine affinity is very strong and it will displace full agonists like heroin and methadone
  - Note receptor binding strength (strong or weak), is **NOT** the same as receptor activation (agonist or antagonist)

Mu Receptor

Bupe affinity is higher

Therefore

Full Agonist is displaced
How Does Buprenorphine Work?

• DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  – Buprenorphine dissociation is slow
  – Therefore buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding
Pharmacology of Full vs. Partial Agonists

- Buprenorphine can precipitate withdrawal if it displaces a full agonist from the mu receptors
- Buprenorphine only partially activates the receptors, therefore a net decrease in activation occurs and withdrawal develops
Suboxone® tabs; films, Zubsolv®

Film strips: 12/3mg, 8/2mg, 4/1mg, and 2/0.5mg

Tabs: 8/2mg, 2/0.5mg, 8 & 2mg monoprodut (Subutex®)

Zubsolv®: 1.4, 5.7mg
New form: Bunavail®
Buccal film strip: less irritating?

More bioavailable:
4.2/0.7mg=8/2mg Sub

Exposure to buprenorphine from BUNAVAIL 4.2/0.7 mg and Suboxone sublingual tablet 8/2 mg was bioequivalent\(^1,2\)
Dosing

• Bioavailability: key
  – Early studies: bioavailability of sublingual liquid buprenorphine at ~50%
  – Methodology flawed: measuring buprenorphine remaining in saliva then deducing absorption
  – Actual measurement: ~30% (Mendelson 1997)
  – Tablet form: only 50% of solution (Noth, Mendelson 1999)
    • Acidification of saliva (coffee, eg): ↓↓
  – Net bioavailability of tablet: ~15%
Dosing (cont)

- Affinity: Higher than other opioids
- (intrinsic) Activity: low, with ceiling effect
- Dissociation: slow (36 hours or longer)
- Therefore, dosing can be daily or every other day for opioid blockade, withdrawal
- However: analgesic effect is short: dosed q6h
- Question: positive reinforcement also q6h?
  - Implications for divided dosing and overuse
Dosing (summary)

- Bioavailability is lower than initially thought
  - Significant variability of bioavailability
- Studies: higher doses ($\geq 16$ mg) = better results
- Dosing limits may be compromising overall effectiveness
  - Balance against diversion risk
- Avoid split-dosing: may contribute to dosing positive reinforcement and overuse
Rationale for Buprenorphine/Naloxone Combination

• When taken sublingually
  – Buprenorphine will be well absorbed
  – Naloxone absorption will be minimal

• If taken intravenously
  – Naloxone now 100% bioavailable
  – In theory: precipitated withdrawal occurs
    • Initial studies: 4:1 ratio: aversive reaction with IV use
  – In practice: need > 10mg Nx IV to precipitate w/d
    • Focus on ↓ diversion rather than aversion

Medelson 2003; Jasinski 1978
Film vs Tablets

- Lintzeris et al 2013: RCT of film vs tablets
  - No significant group differences for
    - Subjective effects
    - Trough buprenorphine levels
    - Adverse events
    - Treatment outcomes
  - Film sig quicker to dissolve (173 v 247s, p=0.007)

- Concern: tablets were crushed, used IN/IV
  - 25%+ increase in bup availability (Middleton, 2011)
Bup Likeability nasally inhaled

Top graph: scale of likeability over time

Bottom graph: perceived street value over time

Square: bup 8mg
Inverted Triangle: bup/nx 8/2mg

(Middleton et al 2011)
Stabilize on Bup, then taper?

- Bup vs Clonidine for Detox: more effective for sx of withdrawal, opioid-free urine and retention in tx
  - Success short-lived: 95% relapse within weeks (Cochrane 2006)
- 2 vs 12 wks stabilize, taper: 6% vs 49% success rate
  - But: after 12 weeks: 92% relapsed
    - No sig benefit of intensive counseling (Weiss et al 2012)
- Time-limited tx (9 mo): after taper, only 12% abstinence at 2 yrs (Korner and Waal 2007)
  - No long-term prospective RCT
Buprenorphine v PCB: Retention in Tx

(Kakko et al., 2003)
Buprenorphine/Nx vs Placebo vs Methadone Maintenance

• Bup, Methadone (MMT) better than placebo
• Initial studies: (Cochrane 2008): MMT higher:
  • retention in tx,
  • more opioid-free urine drug screens
• Later studies: dose dependent, fixed v flexible
  – Low (2-7mg) and medium (8-15mg) bup: inferior to HD methadone (≥85mg) for both measures
  – High fixed-dose buprenorphine (≥16mg): no difference in either measure v HD methadone, both superior to placebo
  • Cochrane 2014
SAMHSA TIP-40: Maintenance Phase

• *May be indefinite: chronic disease model*
• Attention to Psychosocial issues:
  – Psychiatric comorbidity
  – Somatic consequences of drug use (Hep C, eg)
  – Family and relationships
  – Employment and financial issues
  – Legal consequences of drug use
  – Other drug and alcohol use
• Taper based on patient reaching goals, commitment to taper, and physician’s confidence of success of taper.
Discharge

• Taper off, drop out, terminate?
• Goal: retention in treatment: measure of success
  – Why so many rules, if violated, lead to discharge?
  – Diabetes eg: dietary transgressions: d/c insulin?
• Question of motivation: will threats of termination motivate sobriety?
  – No doubt will motivate finding clean urine.
VA Experience

RRC:
Treatment of Opioid Dependence at VAMC-WRJ

• 2008: Modeled “Suboxone® group” after DHMC
  – Efficient
  – Addicts share experiences, group therapy
  – Educates residents, fellows, students

• 2009-14: increased from 15 patients to >145

• Growth: five Suboxone® groups at VA, two at Burlington CBOC (initially tele-psychiatry)
  – Four prescribers facilitate or co-facilitate
2012-2014

• 221 patients treated with Suboxone® maintenance
• 72 discontinued treatment at WRJ VA
  – 31 (14%) tapered off (planned recovery)
    • 4 Transitioned to Naltrexone
    • 2 back on pain meds
    • 9 lost to f/u
  – 21 transferred to other sites still on Suboxone® maintenance
  – 2 transitioned to Methadone Maintenance
  – 7 back on long-acting opioids for chronic pain
  – 1 in jail
  – 1 death
  – 9 dropped out or terminated
    • 5 known relapse (3 op, 1 alc)
• 77% still in treatment with Opioid Agonist Therapy
Buprenorphine Maintenance
VAMC WRJ 2012-2014

221 Patients

72 discontinued at WRJ (33%)
31 (14%) tapered off: planned recovery
16 (7%) successful
2 (1%) on Naltrexone
2 (1%) on Pain Meds
9 (4%) Lost to f/u

21 transferred to other VAs on Bup (10%)
2: back on Pain Meds

11 (5%): other
2: methadone
7: pain meds
1: Jail
1: Death

149 continued at WRJ (67%)
9 (4%) dropped out
5 known relapses
Demographics

- Female: 12/146: 8%
- Age (mean): 40
- Age distribution: bimodal peaks 26-30, 51-55
- Average dose: 16.6mg
- Average length of time on Suboxone: 35 mo.
- Axis I disorder: 90%
  - SMI: Schizophrenia, Schizoaffective d/o: <1% each
- 36% homeless on entry
Age Distribution (n=134)
Co-occurring disorders

Primary Axis I d/o: 90%

- ADHD 3%
- Adjustment d/o 8%
- Anxiety d/o 7%
- Depressive d/o 21%
- PTSD 35%
- BPAD <1%
- Schizophrenia <1%
- None 10%
Culture of Recovery, Transparency

• Suboxone® maintenance is just one part of tx
  – Patients are not terminated for relapse
• Harsh peer feedback for phony UDS
  – High # of screens wear down efforts to conceal
• Peer intolerance of selling/dealing
• “Good Samaritan” approach to divulging relapse of others in the group (vs “ratting out”)

Urine Drug Screens w/Rx

• Last UDS: 45/146 positive : 31%
  • 21% cannabis, 6% opi, 4% amph/coc, 3% bzd

• Behavioral approach
  • 6 clean UDS: advance one week

• Adulteration attempts
  • Urine creatinine, temperature, appearance

• Counterfeit specimens

• Confirmation of all contested results GC/MS
Last Urine Drug Screen

Last UDS: 41+/142=28%

Amp/coc 4%
BZD 3%
Cann 21%
Opi 6%
Neg 69%
Challenges

• Diversion
• Overuse
• Marijuana use: 25% sporadic or more
• Surreptitious alcohol abuse
• Optimal duration of treatment
• Anxiety about tapering off
• Pain control for injury or surgery
Complaints of Diversion

• January-February 2013: 2-3 complaints/week
  – Difficult to verify
  – Retaliation/revenge

• Institution of random pill/strip counts
  – 2/week with spot UDS
  – Serial numbers compared
  – Most common: overuse not diversion
  – Complaints: zero in last six months
Compliance questionnaire

• How do you take your Suboxone® doses? N=100
  – As directed: 65%
  – As needed: 24%
  – Overuse: 10
  – Leftover: 2
• If out, have you bought extra? Yes: 40%
• If extra, have you sold some? Yes: 6%
• Snorted? 1% (vs 18% for tablets 2011)
• Injected? 1%
Marijuana in UDS

• Culture of acceptance especially Vermont
• Medical marijuana
  – Only one patient has valid marijuana card
• Reasons for promoting MJ abstinence:
  – Aharonovich, Liu, Nunes et al, 2005: post-discharge (rehab) cannabis increased 1st use of any substance and reduced likelihood of stable remission
Tx Marijuana Abuse: N=39

- Offered CBT Marijuana Cessation Group:
  - 1/2 travel reimbursement
  - Weekly prescriptions
- Modestly effective:
  - 15 (38%) stopped smoking (2 resumed)
    - 5 from group
    - 7 on their own
    - 3: residential treatment
  - 11: various stages of motivation for change
  - 5 not addressed (4 CBOC, 1 MJ card)
  - 3 dropped out of Suboxone® tx in protest
  - 2 tapered off Suboxone® to smoke; 3 tapering for same
Alcohol consumption

- Ur ETOH, breathalyzer: limited due to volatility
  - Abstention for 24h before results in neg test
- Ethyl Glucuronide Biomarker: urine metabolites
  - Threshold 500 ng/ml
  - More specific than CDT, GGT; past 5-7 days
    - Expensive: $90 send-out
  - Used my own drinking pattern as reference
- 13/92 (14%) unsuspected excessive drinkers
  - 3: ↑ LFTs with hep C: GI said stop Suboxone®
  - 2: residential tx
  - 11: outpatient: 6 stopped, 5 trying
Challenges of Tapering Off

• “Post-acute Withdrawal”: High risk for relapse
  – State of anhedonia, low energy, low motivation
  – Concept: taper slowly
    • 2mg q 2 weeks, 1mg last 2 weeks is tolerated well
    • Encouragement and support

• Concept: Naltrexone after taper
  – Ongoing trials: Mannelli et al

• Concept: Chronic disease model
  – No clinically sig ↑ in LFT’s (Fareed et al 2014)
  – No sig long-term cognitive or psychomotor SE (Shmygalev 2011)
Overuse: 40% in survey

• Unclear reward: ~90% receptors occupied
• Yet, patients insist more gives a “bump” in well-being, energy, motivation
• Extra doses “re-activate” receptor, as for pain?
• Some solutions:
  – Insist on once-daily dosing
  – Locked medication dispenser
  – Employ family member to administer
  – Transition to OTP for daily dispensing or Methadone
  – Transition to Naltrexone
  – Buprenorphine implants?
Buprenorphine Implants

- Ling et al 2010 CTN
- 4-5 80mg implants last 6 months
  - 1-1.3mg buprenorphine/day
  - Plasma levels < trough SL bupe patients
  - RCT: pcb implants, extra buprenorphine as needed
- 71/108 (65.7%) completion in tx group vs 17/55 (30.9%) in pcb group
- 0 tx group vs 30.9% pcb tx failures
Buprenorphine Implant (Ling et al. 2010)
Questions?