Medications to Treat Concurrent Opiate and Cocaine Dependence

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NIDA
Opiate + Cocaine

- “Speedball”
- Combines the effects of both
- Mixture feels “better” - greater level of euphoria
- More medical / psychosocial complications
- Treatment is challenging
Past Year Prevalence of SUD

• Cocaine (n=1.1M)
  – 192,000 (17%) opiate analgesic
  – 121,000 (11%) heroin

• Heroin (n=409,000)
  – 122,000 (30%) cocaine

• Prescription opioid disorder (n=1.8M)
  – 192,000 (10.8%) cocaine

NSDUH, 2009
Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2010

- Alcohol: 2,596,000
- Marijuana: 1,021,000
- Pain Relievers: 754,000
- Cocaine: 699,000
- Heroin: 417,000
- Tranquilizers: 350,000
- Stimulants: 343,000
- Hallucinogens: 333,000
Last/Current Treatment of SUD

- **Cocaine (n=795,000)**
  - 348,000 (44%) opiate analgesic
  - 336,000 (42%) heroin

- **Heroin (n=520,000)**
  - 336,000 (65%) cocaine

- **Prescription opioid disorder (n=755,000)**
  - 348,000 (46%) cocaine

NSDUH, 2009
Medications with Early Efficacy for Cocaine Dependence

- Baclofen: GABA-B receptor agonist
- Modafinil: Dopamine transporter inhibitor enhanced glutamate activity
- Topiramate: Enhance GABA activity, glutamate receptor antagonist
- Disulfiram: Dopamine-β-hydroxylase inhibitor
- Vigabatrin: GABA agonist
- Citalopram: SSRI
- Cocaine vaccine
Opioids – Pharmacological Strategies

• Agonists
  – Methadone
  – LAAM

• Antagonists
  – Naloxone
  – Naltrexone

• Partial agonist/antagonist
  – Buprenorphine
  – Buprenorphine/naloxone

• Symptomatic (opiate withdrawal)
  – Lofexidine
  – Clonidine
Opioid & Cocaine Co-Dependence Potential Pharmacological Strategies

- Mu antagonist / Kappa agonist
  - Nalbuphine

- Mu antagonists
  - Naltrexone

- Partial agonist
  - Buprenorphine

- Opioid agonists
  - Methadone

- Other
  - Amantadine, lofexidine, etc
Nalbuphine

- kappa agonist/partial mu antagonist analgesic
- Low abuse liability
- Long duration of analgesic action (IM, IV, SC)
- Significant and sustained reductions in cocaine self-administration by rhesus monkeys without altering food-maintained responding
  (Negus and Mello, 2002)
- Dose-dependent downward shifts in the cocaine self-administration dose–effect curve
  (Negus and Mello, 2002)
- May precipitate opiate withdrawal
Naltrexone 50 mg and relapse prevention therapy evidenced significantly fewer cocaine-positive urines than participants receiving other treatment combinations (RP: Relapse Prevention, DC: Drug Counseling).
Buprenorphine

• Partial mu-opioid receptor agonist
• Weak delta-receptor agonist
• Activates ORL-1 receptor
• Marketed worldwide as an analgesic
• Approved in the U.S. and other countries for tx of opiate dependence, 8-16 mg/d
Animal Studies – in favor

- Decreases cocaine self-administration in rhesus monkeys (Mello et al, 1989; Lukas, 1995) and rats (Carroll, 1992)
- Reduces long-term (1-4 months) cocaine self-administration in rhesus monkeys (Kamien, 1991; Mello, 1992)
- Blocks cocaine induced place preference (Suzuki, 1992; Kosten, 1991)
- Reduces hole-dipping behavior in mice (Suzuki, 1993; Jackson, 1993; Calcagnetti, 1995)
- Synergism with cocaine on rotational behavior in rats (Kimmel, 1997)
- Suppresses behavior reinforced by smoked cocaine in monkeys (Carroll, 1992)
- Prevents reinstatement of responding produced by cocaine in rats (Comer, 1993)
- Protective effect against combined cocaine-ethanol lethality (Hayase, 1996)
- Decreases cocaine's reinforcing properties more effectively than naltrexone in monkeys (Mello, 1990)
- Intermittent buprenorphine treatment is less effective than daily treatment in reducing cocaine self-administration by rhesus monkeys (Mello, 1993)
- Attenuated cocaine-induced release of plasma lactate dehydrogenase (LDH) in mice (Shukla, 1991)
Animal Studies - Against

- Increased conditioned place preference in non-human primates => may potentiate cocaine effect and enhance rewarding properties of cocaine (Brown, 1991)

- Small alterations in cocaine's discriminative stimulus effects in rats (Dykstra, 1992)

- Little effect on cocaine base smoking. However, bup+reinforcers more effective (Rodefer, 1997)

- Neither reversed nor enhanced cocaine's behavioral effects (Crowley, 1993)

- Dose-dependent protection against the lethal effects of cocaine in mice (Witkin, 1991)
Human Laboratory Studies

In Favor

- Decreased cocaine self-administration in humans when 16- or 32-mg doses were available, but not when 48 mg was available (Foltin, 1996)
- 4 mg/day sublingually suppressed acute cocaine-induced stimulation of both ACTH and euphoria (Mendelson, 1996)
- Reversed the P300 amplitude decrement following detoxification => effective in eliminating detoxification-induced impairments (Kouri, 1996)

Against

- 2 mg/d sublingually and cocaine challenges (2 mg/kg): enhanced patients' ratings of cocaine-induced pleasurable effects, and augmented cocaine-induced pulse increases (Rosen, 1993)
Clinical Studies
In Favor

• Cocaine abuse was five to eight times lower than with methadone treatment (n=138) (Kosten, 1989)

• Larger reduction in cocaine abuse at 6 mg than at 2 mg daily (Kosten, 1996)

• Buprenorphine (4, 8, 12, 16 mg) for 21 days had less robust impact on cocaine use than heroin; higher doses and longer time led to attenuated cocaine use (Schottenfeld, 1993)

• Buprenorphine (2, 8, or 16 mg daily, or 16 mg on alternate days) for 70 days (N=200). At 16 mg daily well tolerated and effective in reducing concomitant opiate and cocaine use (Montoya, 2004)
Buprenorphine Changes in Cocaine Use

Montoya et al, 2004
Clinical Studies

Inconclusive

- Average doses achieved 11.2 mg buprenorphine and 66.6 mg methadone (26 weeks): Bup greater proportion of negative urine samples, in particular cocaine-negative samples, compared with methadone, although not statistically significant (Strain, 1994)

- Buprenorphine (N = 43; average dose = 9.0 mg/day sublingually) methadone (N = 43; average dose = 54 mg/day orally) for 16 weeks: A trend toward continued improvement in opioid-positive urines over time was noted for the buprenorphine but not the methadone group (Strain, 1996)

- Buprenorphine (8 mg) group provided a greater proportion of negative urine samples (24 weeks), in particular cocaine-negative samples, compared with the methadone group, not statistically significant (Eder, 1998)
Clinical Studies Against

• Buprenorphine (12 or 4 mg) vs methadone (65 or 20 mg): (24 weeks) do not support the superiority of buprenorphine compared with methadone for reducing cocaine use (Schottenfeld, 1997)

• Buprenorphine (12-16 mg) or methadone (65-85 mg p.o.) and to contingency management or performance feedback for 24 weeks (n=162). Methadone may be superior to buprenorphine for maintenance treatment of patients with co-occurring cocaine and opioid dependence. Combining methadone or buprenorphine with contingency management may improve treatment outcome (Schottenfeld, 2005)
Methadone vs Buprenorphine for “Speedball” Dependence

Schottenfeld, 2005

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**Graph:**

- **Cumulative Proportion of Subjects Remaining in Treatment**
- **Time (weeks):** 0, 3, 6, 9, 12, 15, 18, 21, 24

- **Lines and Descriptions:**
  - Red dashed line: Methadone plus performance feedback (N=40)
  - Red line: Methadone plus contingency management (N=40)
  - Green dashed line: Buprenorphine plus performance feedback (N=43)
  - Green line: Buprenorphine plus contingency management (N=39)

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*a* Significant differences in retention between subjects who received methadone and subjects who received buprenorphine (log rank = 6.4, df=1, p<0.05).

Schottenfeld, 2005
Secondary Analysis

In Favor
- Oliveto et al., 1999
- Lavignasse et al., 2002
- Thirion et al., 2000
- Fudala et al., 2003
- Vigezzi et al., 2006
- Cozzolino et al., 2006

Inconclusive
- Johnson et al., 1995b
- O'Connor et al., 1998
- Johnson et al., 2000
- Perez de los Cobos et al., 2000
- Schottenfeld et al., 2000
- George et al., 2000
- Petitjean et al., 2001
- Kosten et al., 2003
- Mattick et al., 2003
- Gerra et al., 2006
- Fiellin et al., 2006

Against
- Stine and Kosten, 1994
- Johnson et al., 1995a
- Ling et al., 1996
Fudala, Bridge, et al. 2003
Bup+Naloxone
N=472
Figure 2b  Rates (%) of positive urines for cocaine metabolites in group A (naltrexone alone) and group B (naltrexone plus buprenorphine) patients at week 1, 4 and 12
Buprenorphine + Naltrexone

- **Buprenorphine pharmacology**
  - Partial agonist at mu opioid receptor (MOR)
  - Antagonist at kappa opioid receptor (KOR)
  - Agonist at ORL-1 (opioid receptor-like1) Nociceptin NOR

- **Naltrexone pharmacology**
  - Partial agonist/antagonist at KOR and delta Opioid receptor (DOR)
  - No activity at ORL-1

- **Naltrexone + Buprenorphine provides KOR antagonist with ORL-1 (nociceptor) agonist activity**

This slide adapted from Alkermes slide 2011
Buprenorphine + Naltrexone
(Jones et al, unpublished)

Study Days-
-20 to -2  screening
-1  Hospital entry
1  Naltrexone 25 mg
2  Naltrexone 50 mg daily
3  Randomization
4  Buprenorphine
6  Buprenorphine
8  Buprenorphine
10  Buprenorphine,
Naltrexone stopped
11  Hospital discharge
16-24  Follow-up visit

- Eight healthy volunteers
- Very little opiate experience
- 12 inpatient days
- Naltrexone 50 mg daily
- Every two days
  - Bup 0, 4, 8, 16 mg
  - (as Suboxone, blind, order balance)
- Symptom reports
- CV and respiratory indices
- Pupil size and skin T
- Pharmacokinetics
**VAS Reported Symptoms**  0-100 scale

**VAS “Liking”**

- Time Relative to Challenge (Hr)
- Mean VAS Like Score
- Line 1, Line 2, Line 3, Line 4

**VAS “High”**

- Time Relative to Challenge (Hr)
- Mean VAS High Score
- Placebo, 4/1 mg Suboxone, 8/2 mg Suboxone, 16/4 mg Suboxone

**VAS “Good Effects”**

**VAS “Good Effect”**

**VAS “Drug Effect”**

- Time Relative to Challenge (Hr)
- Mean VAS Drug Score
- Placebo, 4/1 mg Suboxone, 8/2 mg Suboxone, 16/4 mg Suboxone

*Jones et al, unpublished*
Results

• Treatments well tolerated, no safety issues
• No statistically significant difference between placebo and any buprenorphine dose, on any measure
• No convincing trends toward unblocked bup effects on any measure
• Nobody liked buprenorphine
• No PK interactions evident
• Outpatient administration of a bup-naltrexone 8/50 mg combination is feasible

Jones et al, unpublished
Buprenorphine + Naltrexone
CURB study (n=300)
Conclusion

• Concurrent opiate and cocaine dependence is a significant public health problem and difficult to treat

• No conclusive efficacy of medications

• Buprenorphine appears promising

• Less evidence with methadone

• Buprenorphine/naloxone + naltrexone may be a good option to treat cocaine dependence in patients detoxified from opiates
Other Txs

• Lofexidine: attenuates stress-induced reinstatement of “speedball” seeking rats (Highfield, 2001)

• Fluopenthixol (non-selective DA antagonist) + quadazocine (opioid antagonist): antagonize reinforcing effect of speedball in rhesus monkeys (Mello, 1999)

• Indatraline (DA reuptake inhibitor) + buprenorphine reduce “speedball” self-administration in rhesus monkeys
Cocaine – Pharmacological Strategies

• Direct Action on the Dopamine System
  – Dopamine Transporter
  – Dopamine Receptor Subtypes

• Indirect Modulation of the Dopamine System
  – Serotonin
  – Opioid
  – GABAergic
  – Glutamate
  – Endocannabinoid
  – Neuropeptides

• Other
Amantadine

No statistically significant differences

Perez de los Cobos et al. 2001
Opiate + Cocaine

- Preclinical studies demonstrate that cocaine and heroin potentiate the reinforcing effects of one another in the self-administration paradigm [Mattox et al., 1997, Rowlett and Woolverton, 1997]

- The combination of cocaine-induced competitive inhibition of DAT and the increase in the DA release elicited by heroin is responsible for the synergistic increase in DA, induced by speedball (Lindsay et al, 2011).

- Dopamine and μ-opiate receptors in the nucleus accumbens are involved in the reinforcing effects of speedball
Neurotoxicity of heroin–cocaine combinations in rat cortical neurons (Cunha-Oliveira et al, 2010)

- Combination of cocaine and heroin:
  - Potentiates neuronal cell death
  - Induces a higher degree of mitochondrial dysfunction
  - Induces apoptotic hallmarks
  - Shifts cell death mechanisms towards necrosis
Nalmefene

- Primarily mu-opioid receptor antagonist; however:
- Few reports suggesting that may also have agonist, or partial agonist properties at kappa-opioid receptors
- May be useful for cocaine dependence