Medications to Treat Concurrent Opiate and Cocaine Dependence

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Opiate + Cocaine

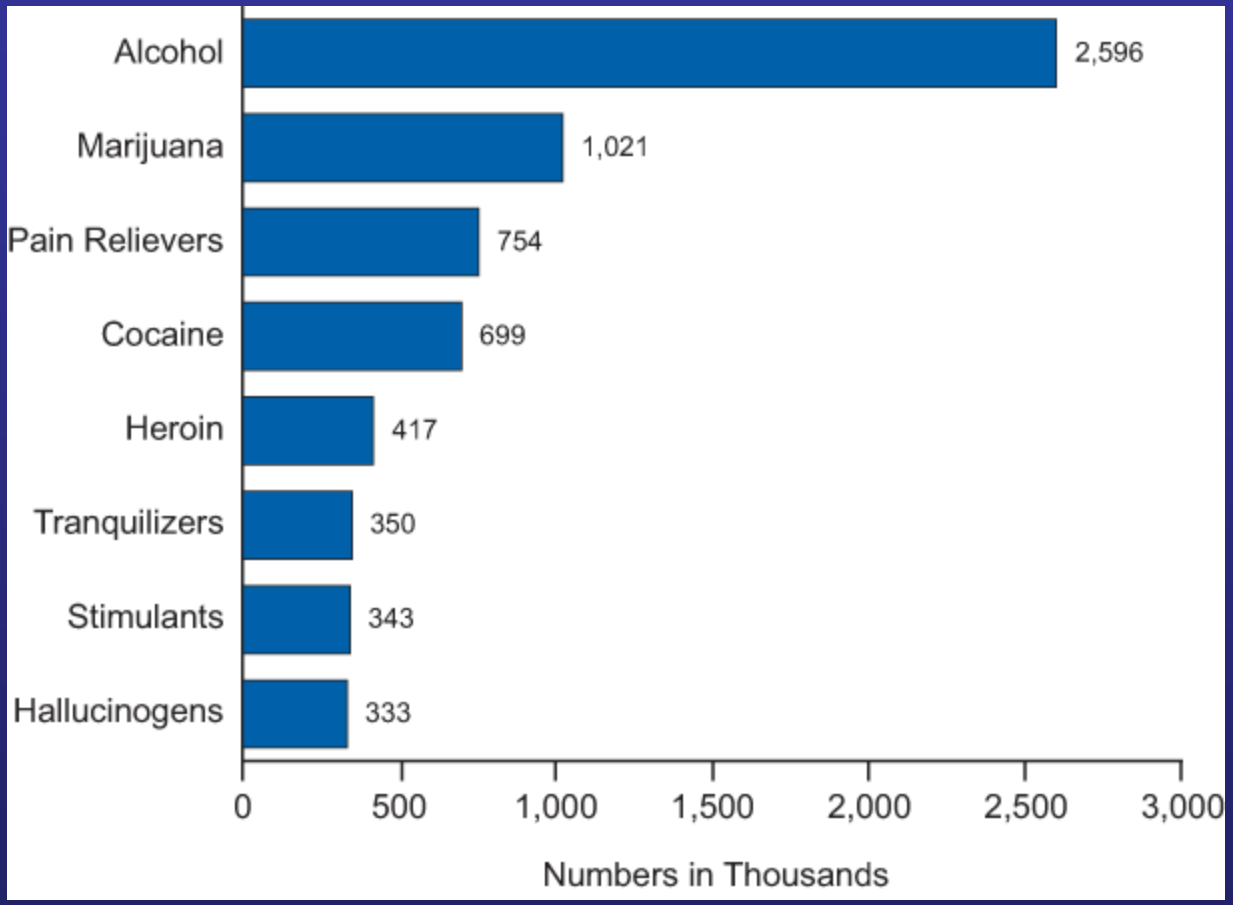
- “Speedball”
- Combines the effects of both
- Mixture feels “better” - greater level of euphoria
- More medical / psychosocial complications
- Treatment is challenging

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



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
• Vigabatrim	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

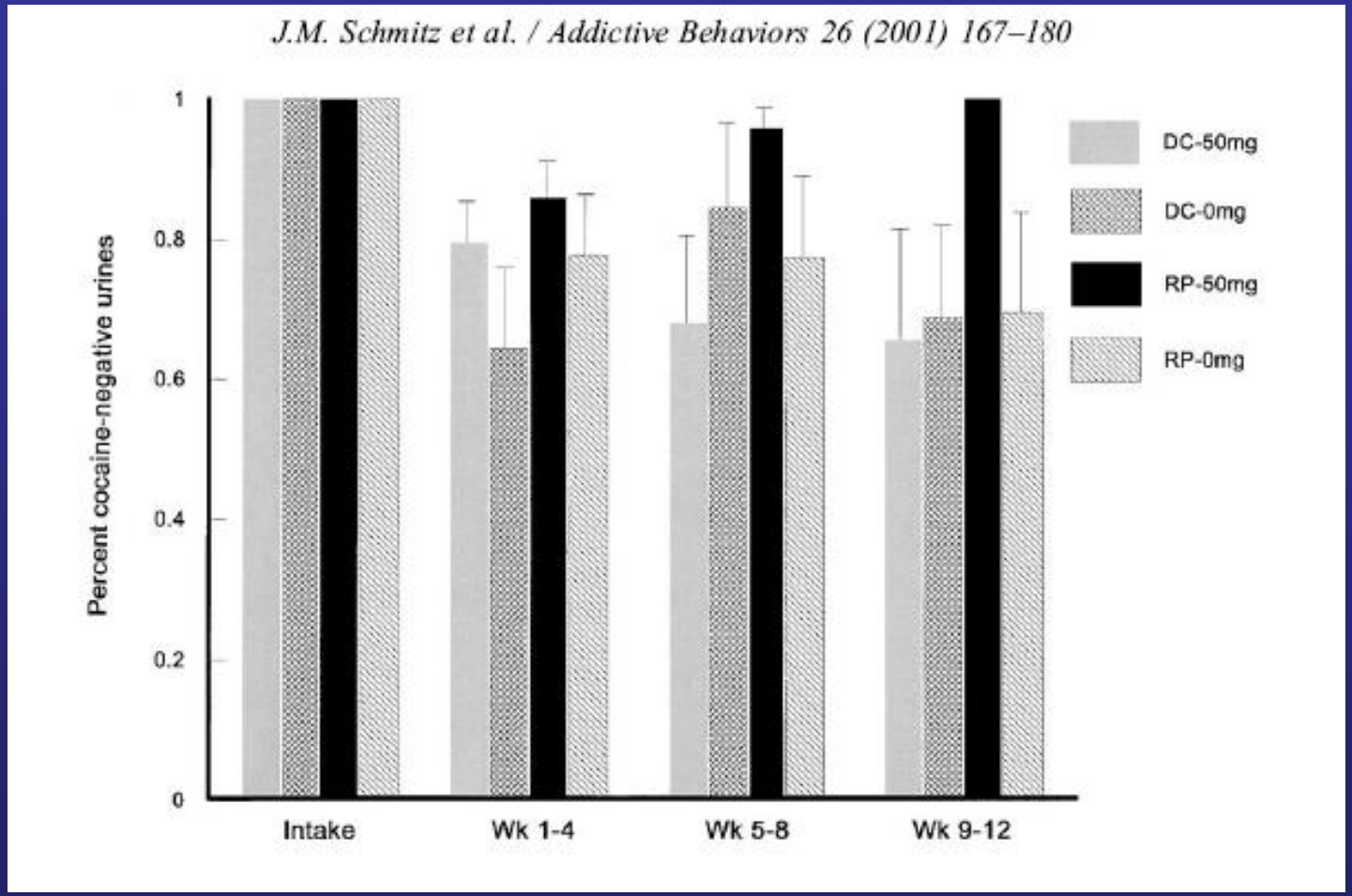
Nalbuphine

- 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



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)

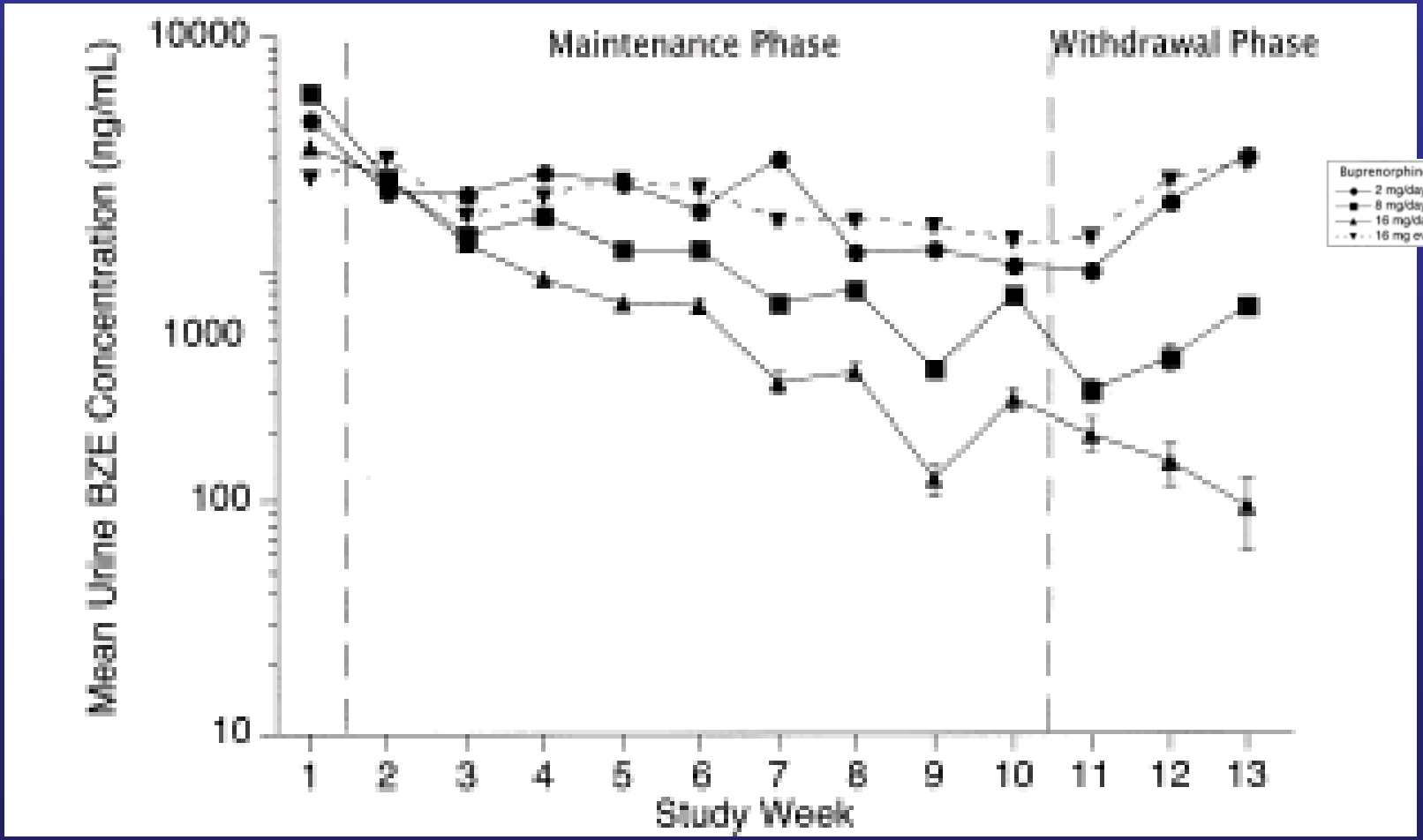
Against

- 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)

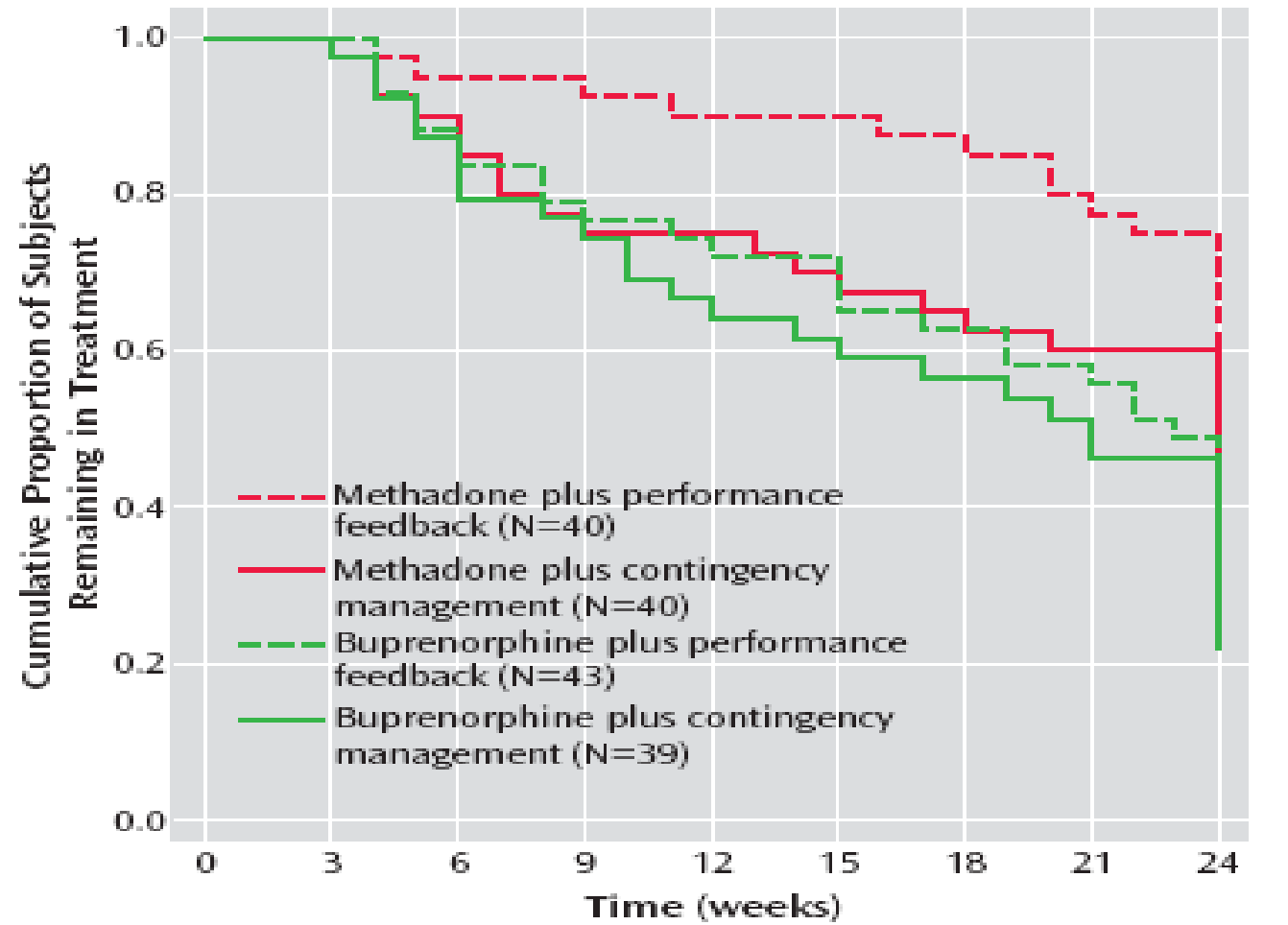
- Buprenorphine (8 mg) group provided a greater proportion of negative urine samples (24 weeks), in particular cocaine-negative samples, compared with the methadone group, not statistically significant (Eder, 1998)

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



[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

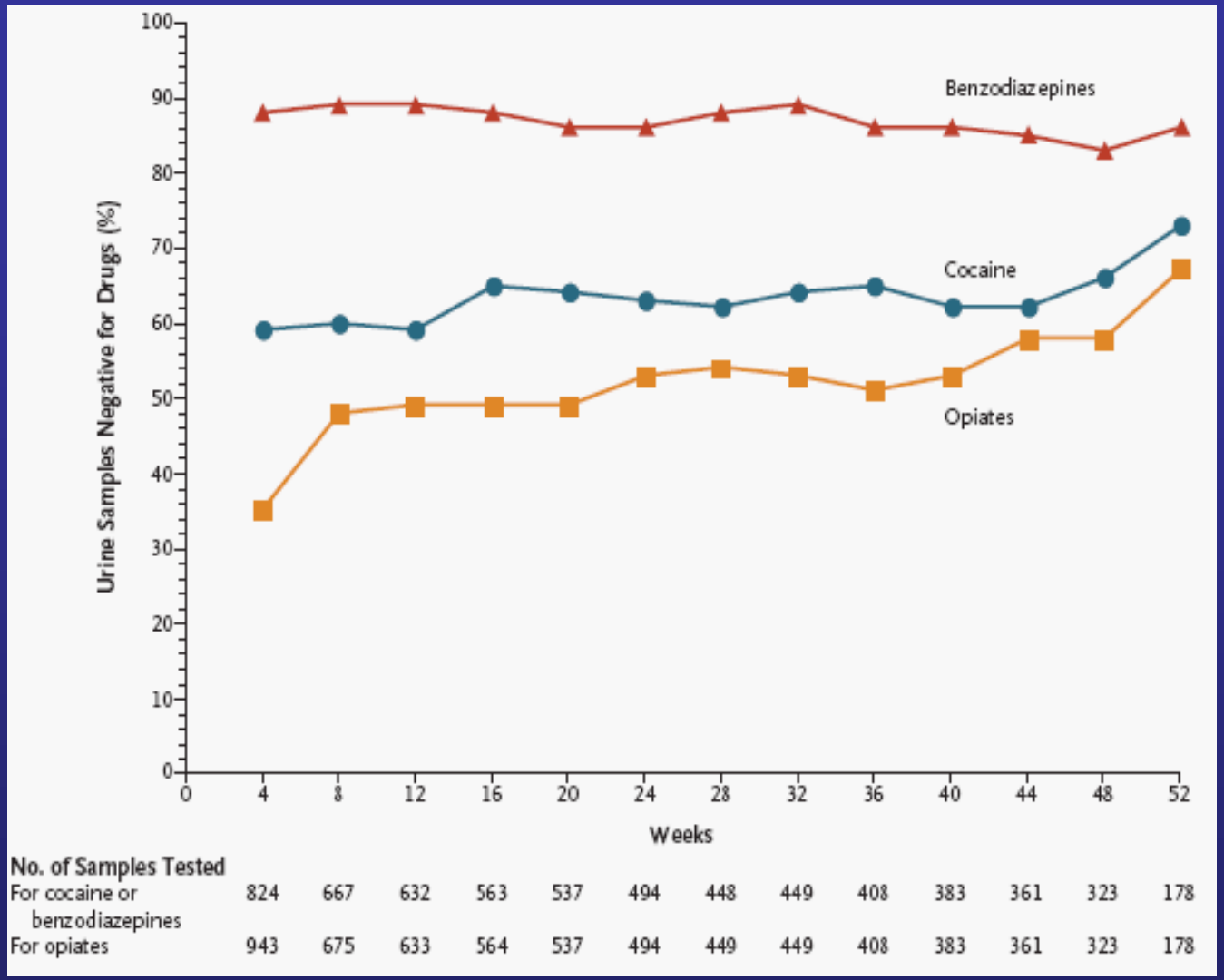
- Oliveto et al., 1999
- Lavignasse et al., 2002
- Thirion et al., 2000
- Fudala et al., 2003
- Vigezzi et al., 2006
- Cozzolino et al., 2006

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

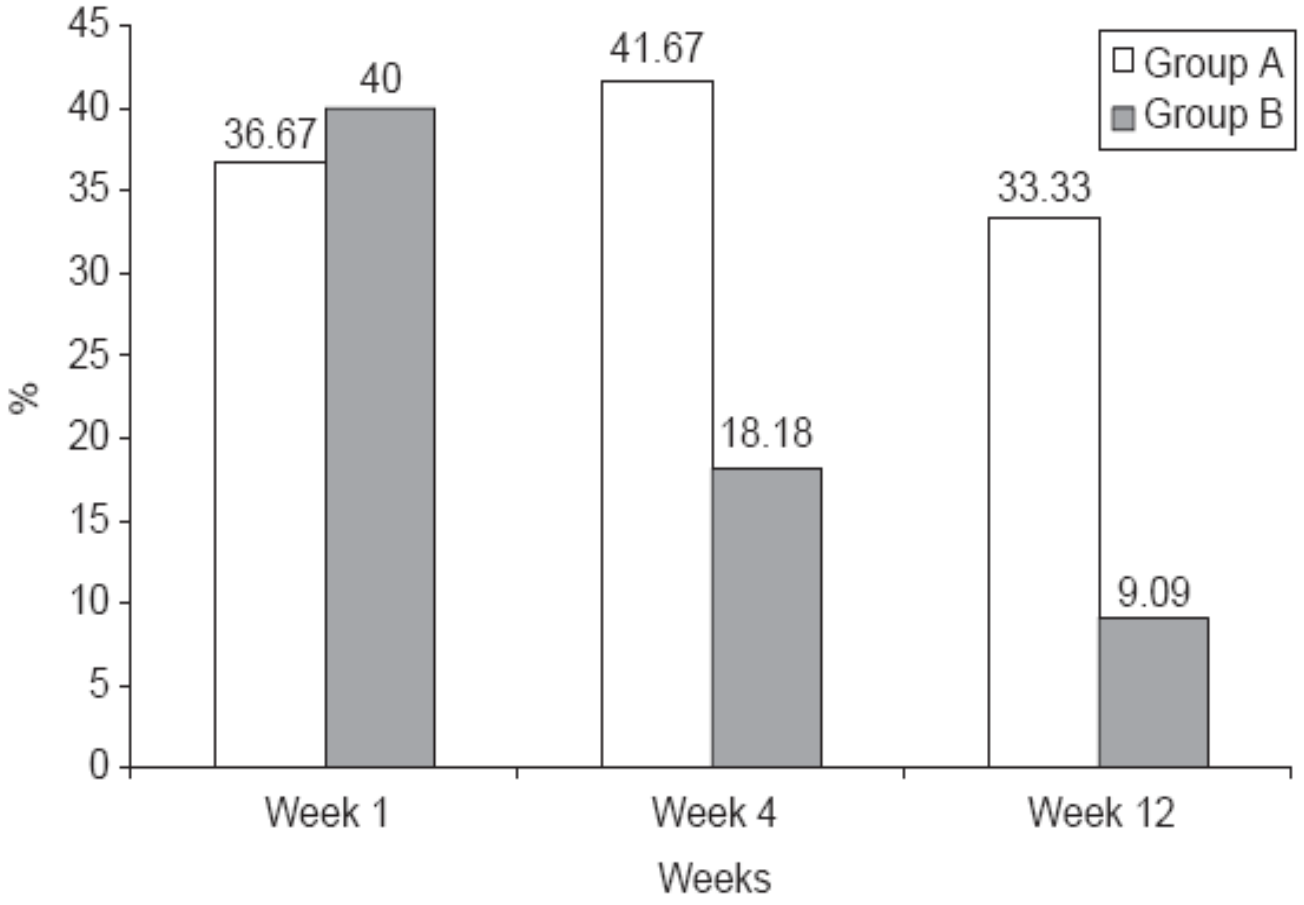
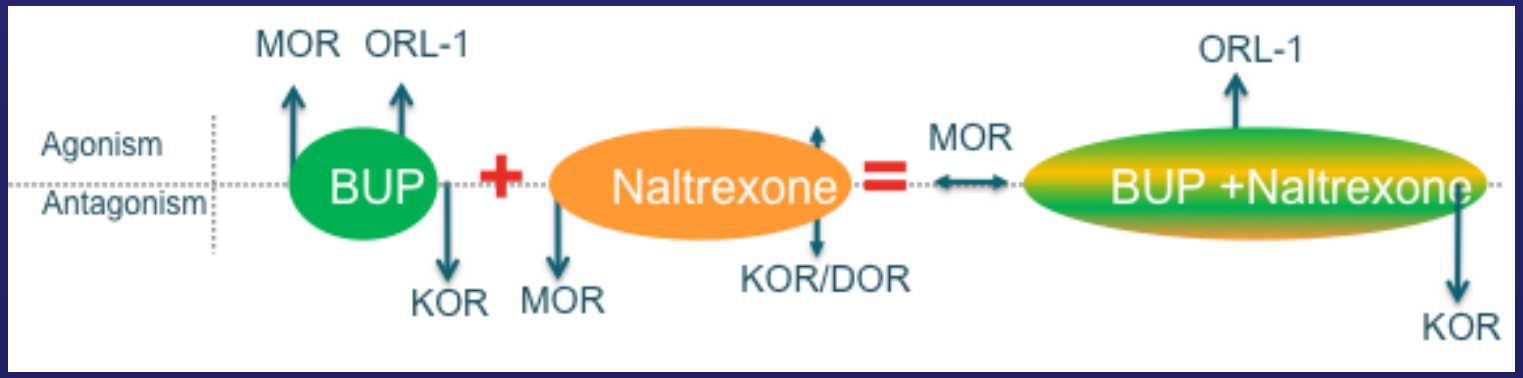


Figure 2b Rates (%) of positive urines for cocaine metabolites in group A (naltrexone alone) and group B (naltrexone plus buprenorphine) patients at week 1, 4 and 12

(Gerra et al., 2006)

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

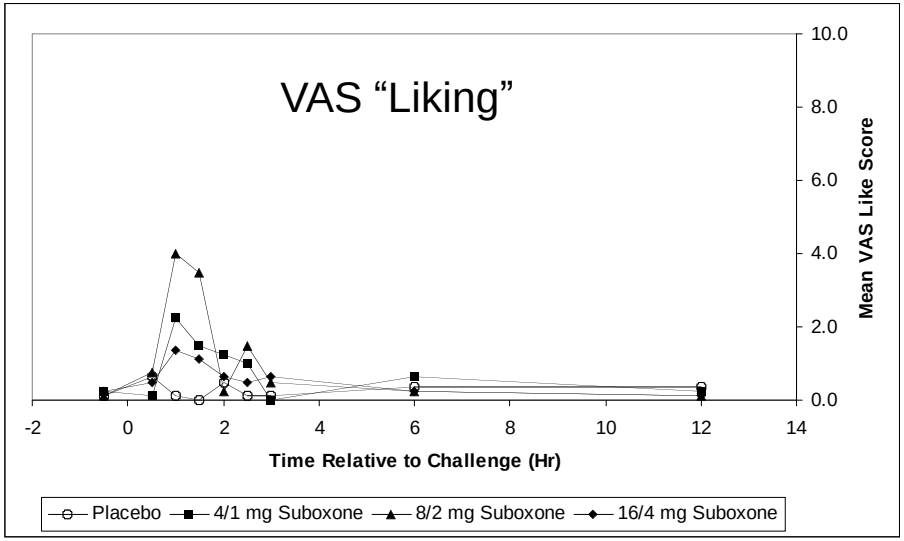
(Jones et al, unpublished)

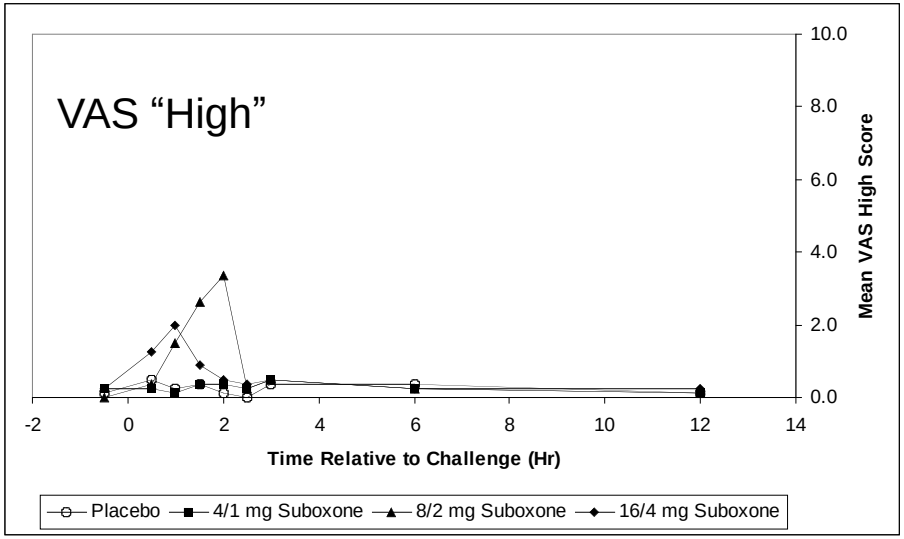
Study Days-

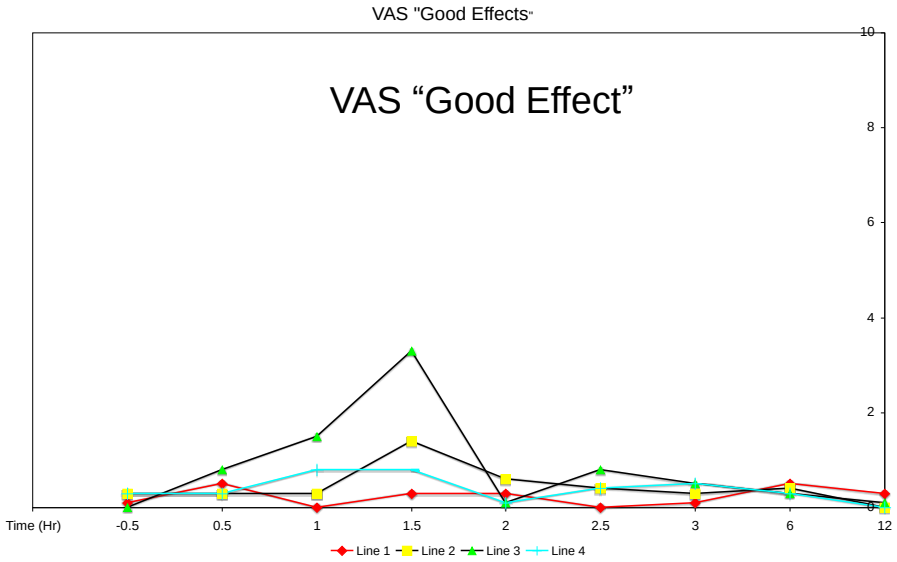
-20 to -2	screening
-1	Hospital entry
1	Naltrexone 25 mg
2	Naltrexone 50 mg daily
3	Randomization
4	Buprenorphine
6	Buprenorphine
8	Buprenorphine
10	Buprenorphine, Naltrexone stopped
11	Hospital discharge
16-24	Follow-up visit

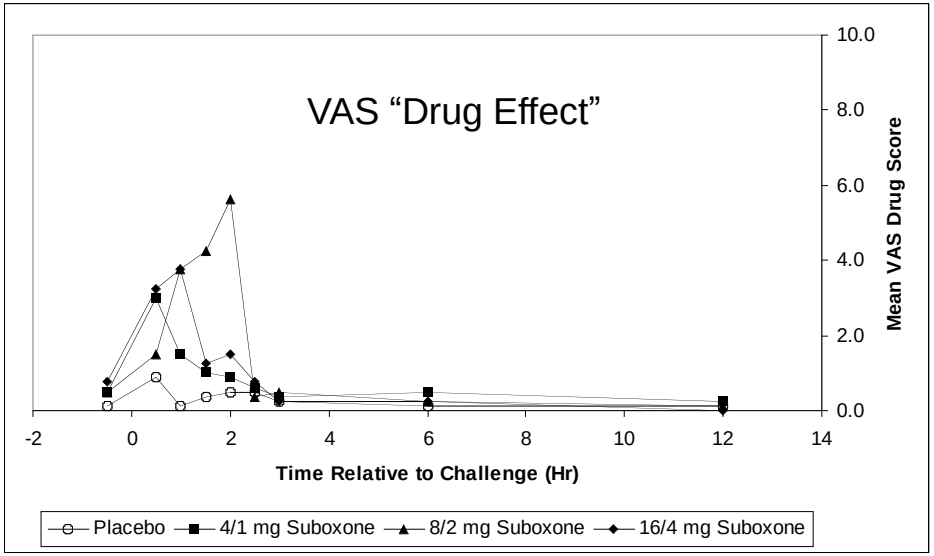
- Eight healthy volunteers
- Very little opiate experience
- 12 inpatient days
- Naltrexone 50 mg daily
- Every two days
  - Bup 0, 4, 8, 16 mg
  - (as Suboxone, blind, order balance)
- Symptom reports
- CV and respiratory indices
- Pupil size and skin T
- Pharmacokinetics

VAS Reported Symptoms 0-100 scale









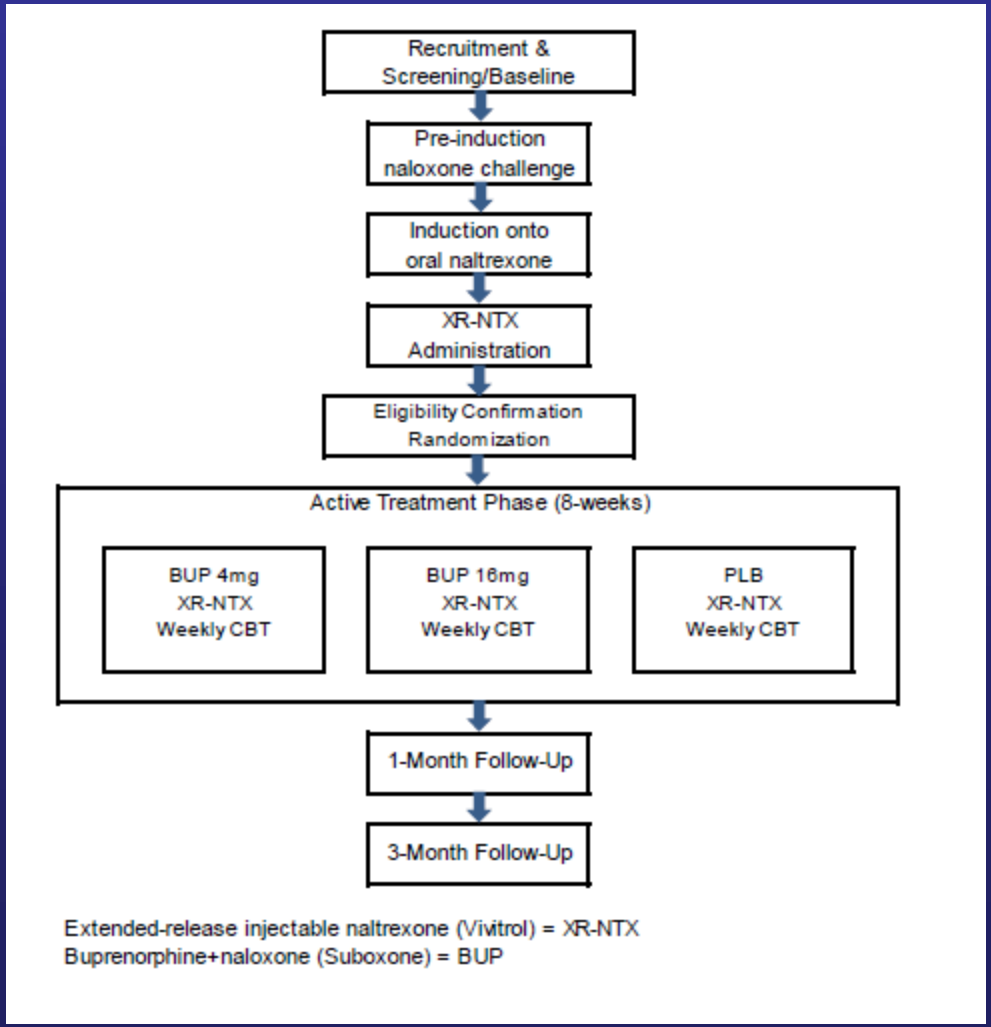
Jones et al, unpublished

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

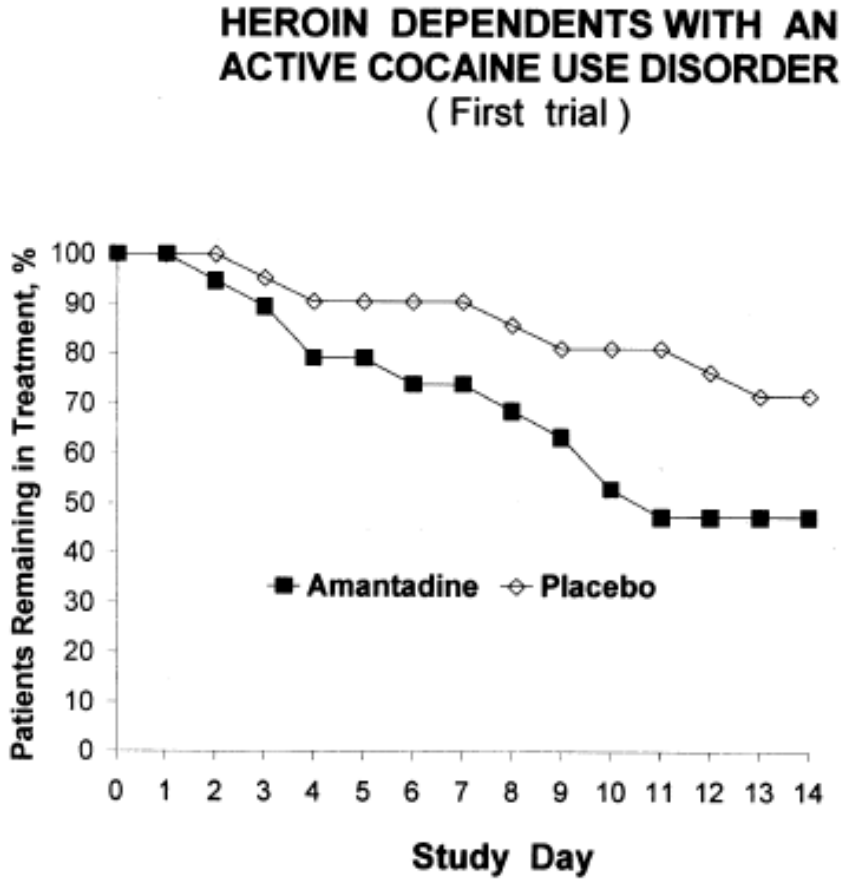
Other Txs

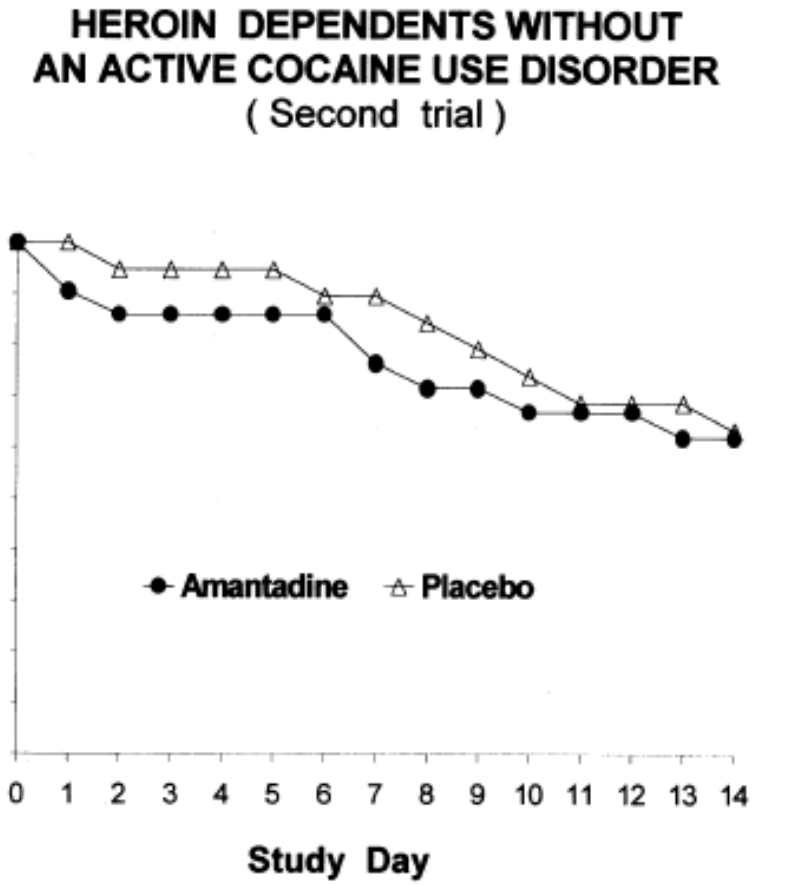
- Lofexidine: attenuates stress-induced reinstatement of “speedball” seeking rats (Highfield, 2001)
- Fluopenthixol (non-selective DA antagonist) + quadazocine (opioid antagonist): antagonize reinforcing effect of speedball in rhesus monkeys (Mello, 1999)
- Indatraline (DA reuptake inhibitor) + buprenorphine 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

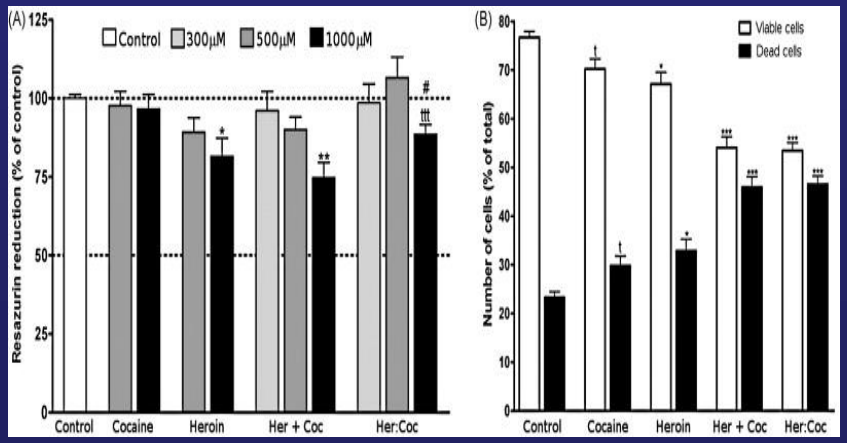
- Preclinical studies demonstrate that cocaine and heroin potentiate the reinforcing effects of one another in the self-administration paradigm [Mattox et al., 1997 ,Rowlett and Woolverton, 1997]

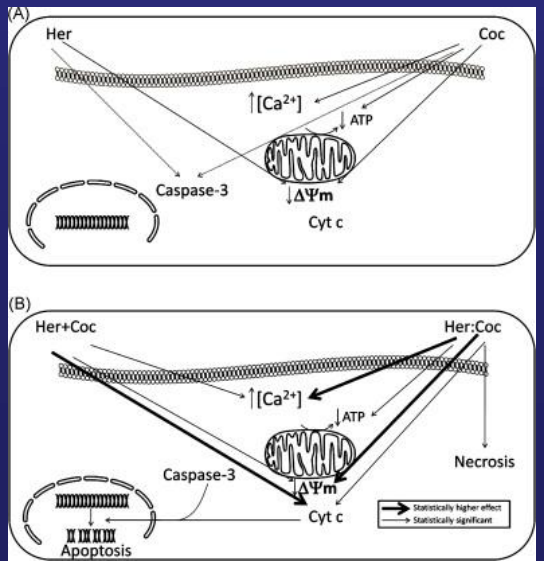
- The combination of cocaine-induced competitive inhibition of DAT and the increase in the DA release elicited by heroin is responsible for the synergistic increase in DA, induced by speedball (Lindsay et al, 2011).

- 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