Overview of Addiction Relapse Prevention Medications

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Health Networks
Learning
Collaborative

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Conceptual Issues

- Should medications be used in the treatment of addiction?
  - Is this a philosophical question?
  - Is this a scientific question?
  - Is this a practical question?

The power of language

- Mind altering substances
- “Drug-free” treatment
- “Abstinence-based” treatment
- Medication assisted treatment
- Medication assisted recovery
- Counseling-assisted medication
- Relapse-prevention medications

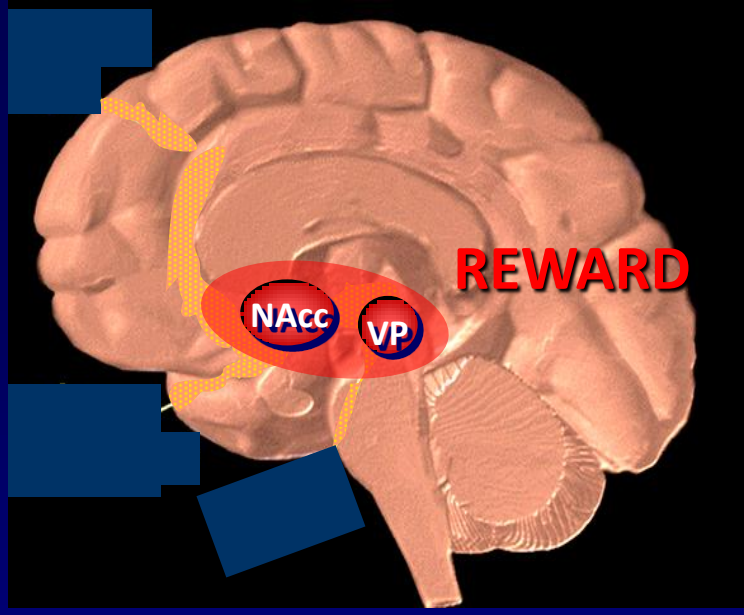
Rationale for medication

- Reduce craving
- Impact the physiology of dependence
- Protect against lapses, which should be expected
- Reduce high rates of relapse
- Improve treatment retention
- Improve outcomes of current psychosocial treatments

Anti-addiction medications - potential effects

- Block the effects of action
- Reduce reward
- Prevent withdrawal
- Act as non-impairing substitute
- Enhance negative consequences
- Prevent relapse after abstinence

Reward Circuits

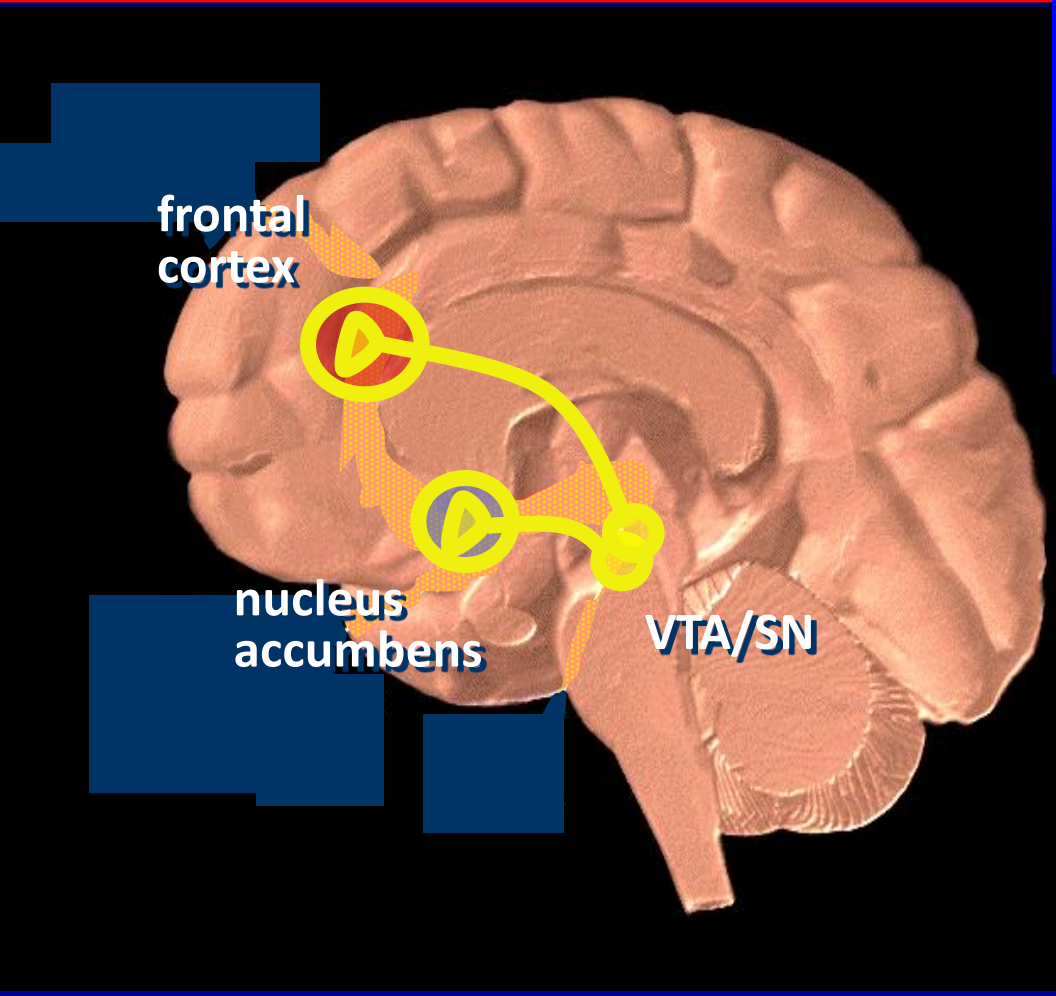


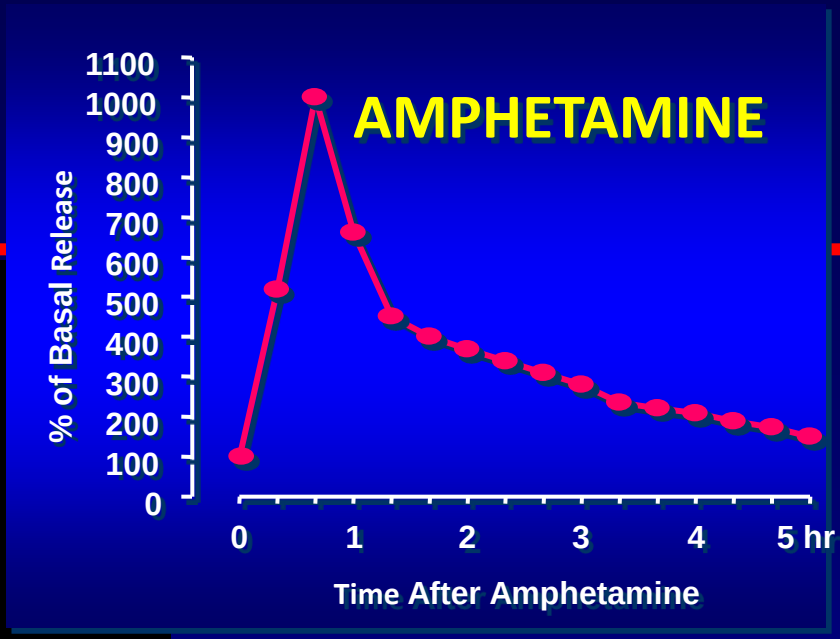
Drugs of Abuse Engage Systems in the *Motivation Pathways* of the Brain

Vocabulary

- Agonist - drug that activates a receptor
- Antagonist - drug that blocks a receptor
- Partial agonist/antagonist - drug that does some of both

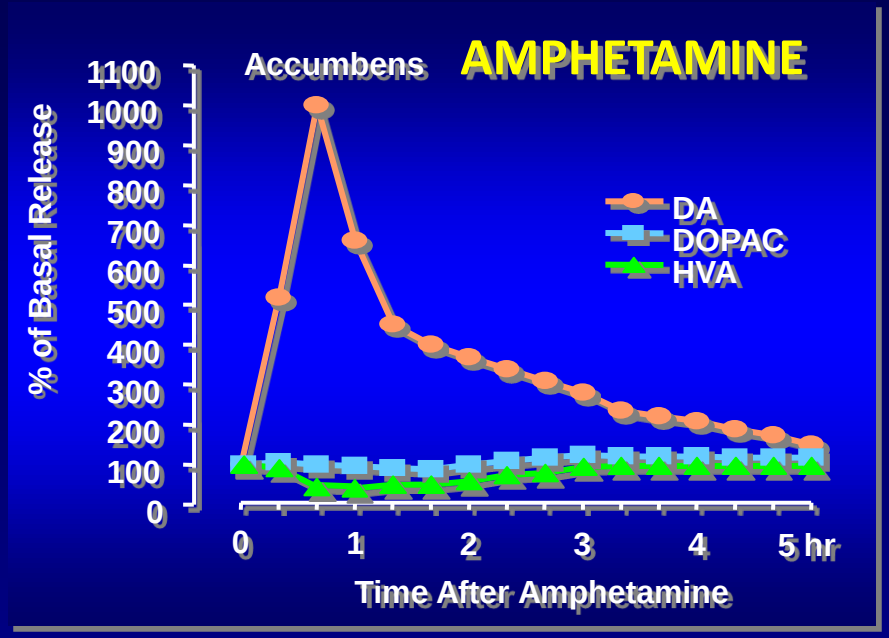
Drugs of Abuse Cause a Release of Dopamine

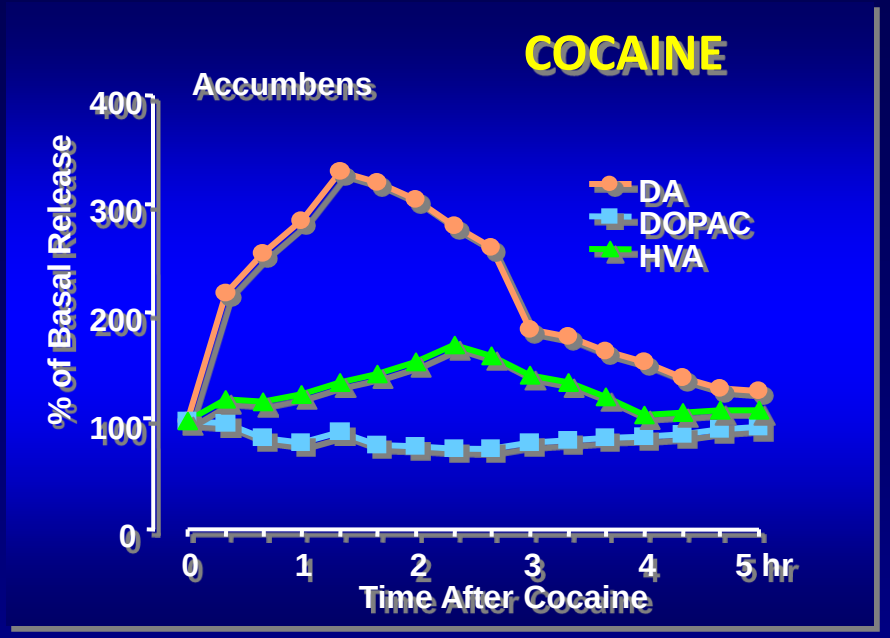


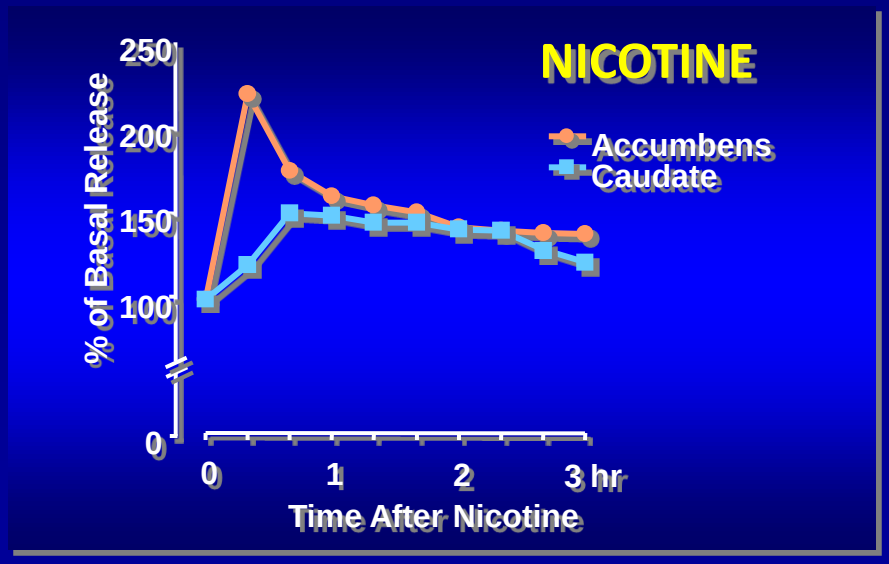


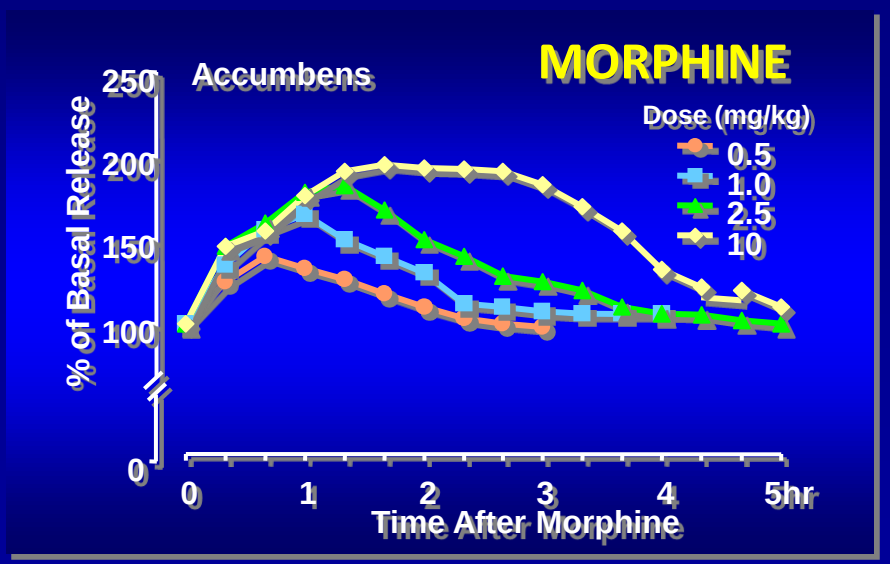
SOURCE: Di Chiara et al

Drugs of Abuse Cause a Release of Dopamine

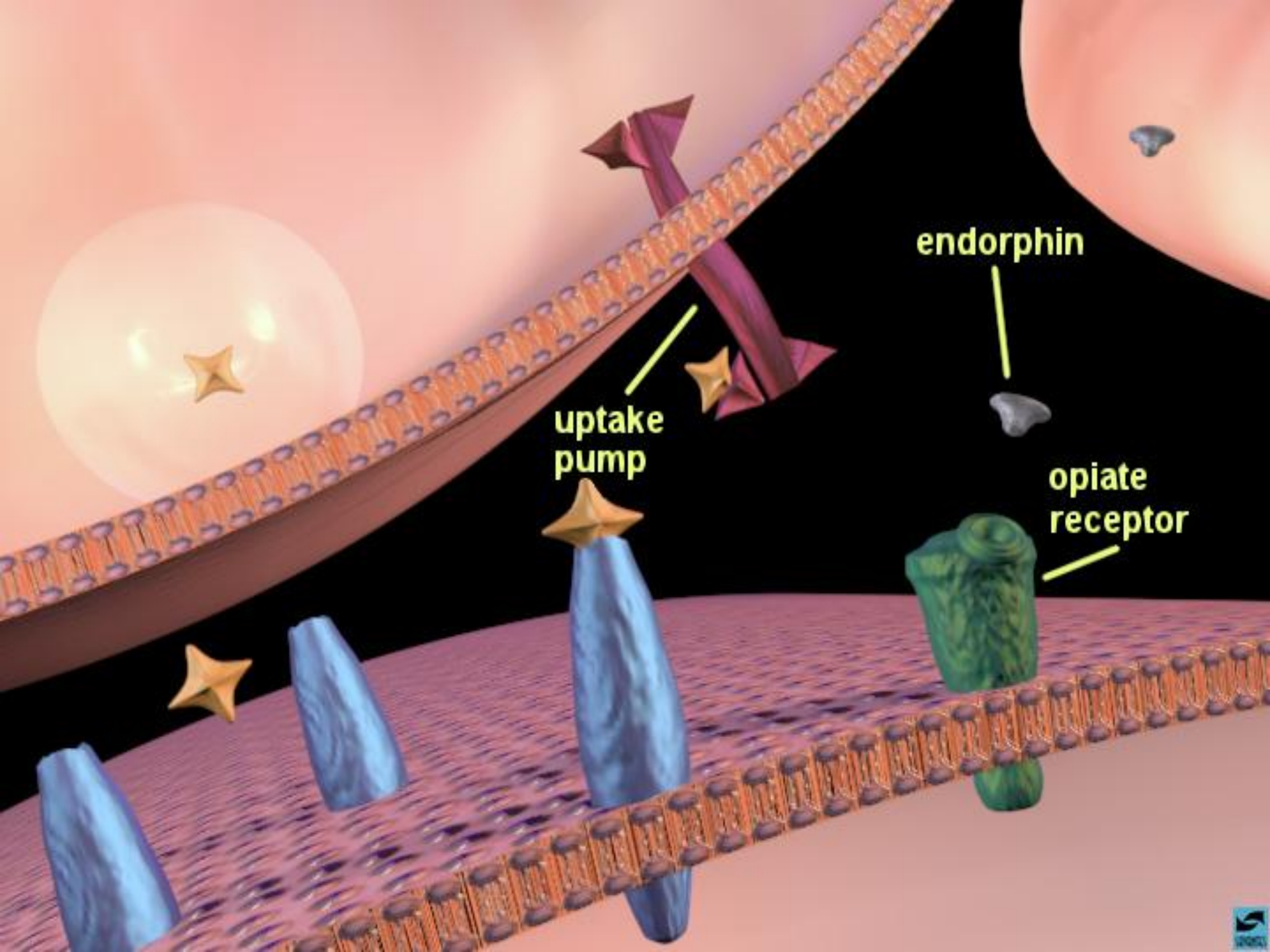


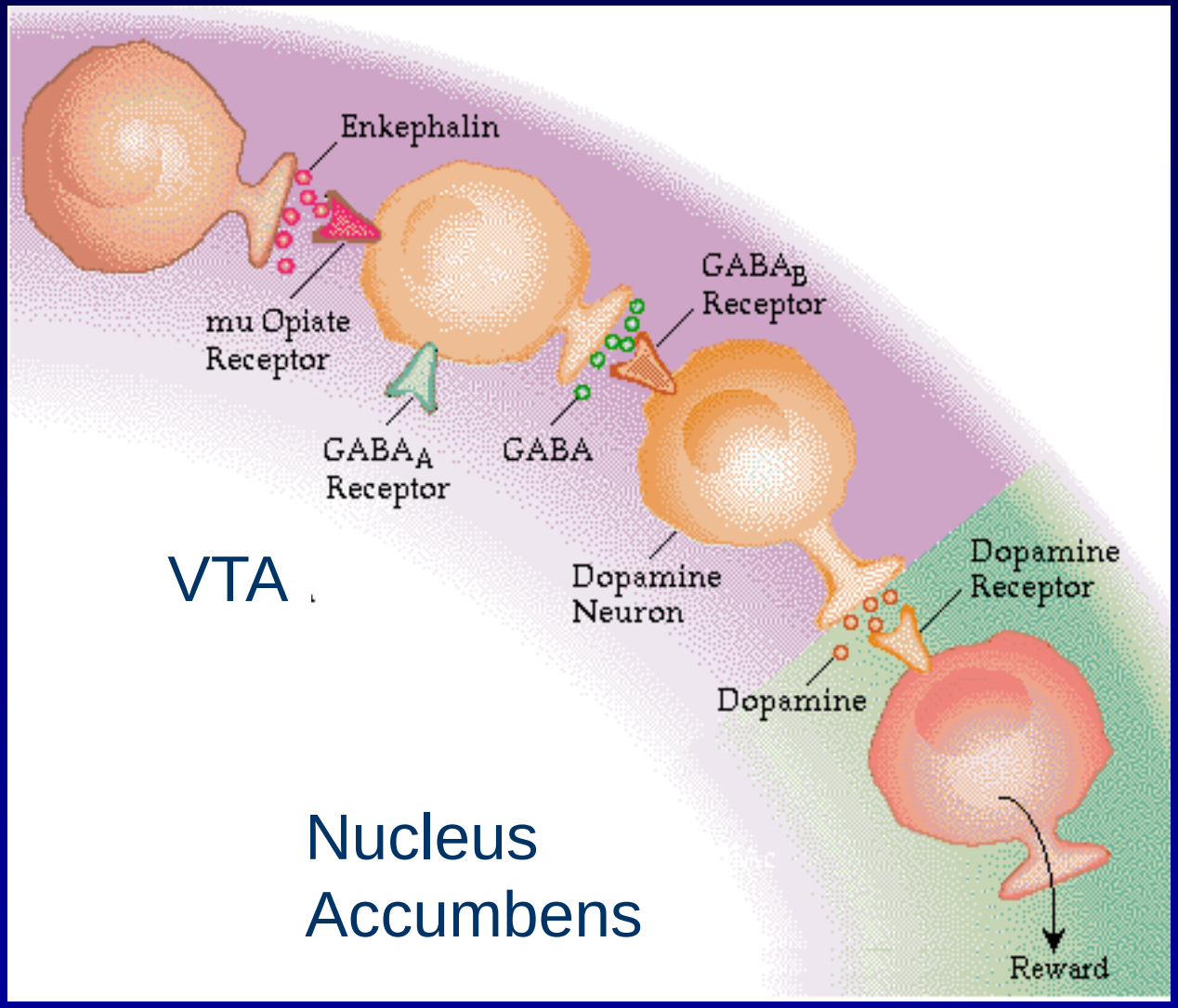






SOURCE: Di Chiara and Imperato


endorphin
uptake pump
opiate receptor


Enkephalin
mu Opiate Receptor
GABA$_A$ Receptor
GABA
GABA$_B$ Receptor
Dopamine Neuron
Dopamine Receptor
Dopamine
Reward
VTA
Nucleus Accumbens

Vocabulary

- Craving - subjective sense of hunger for substance
- Triggers – salience of environmental cues, associated with behaviors (conscious or unconscious)
- Reinforcement - response that increases likelihood of behavior
- Positive reinforcement - positive stimulus (reward craving) that increases likelihood of behavior
- Negative reinforcement - removal of noxious stimulus (relief craving) that increases likelihood of behavior
- Punishment - noxious stimulus that decreases likelihood of behavior

Multiple Mechanisms of Action

- Agonists
- Antagonists
- Modulators of reinforcement pathways
- Aversive agents
- Modulators of metabolism
- Immunization
- Modulators of sustaining or re-instatement pathways
- Others?

Conceptual underpinnings

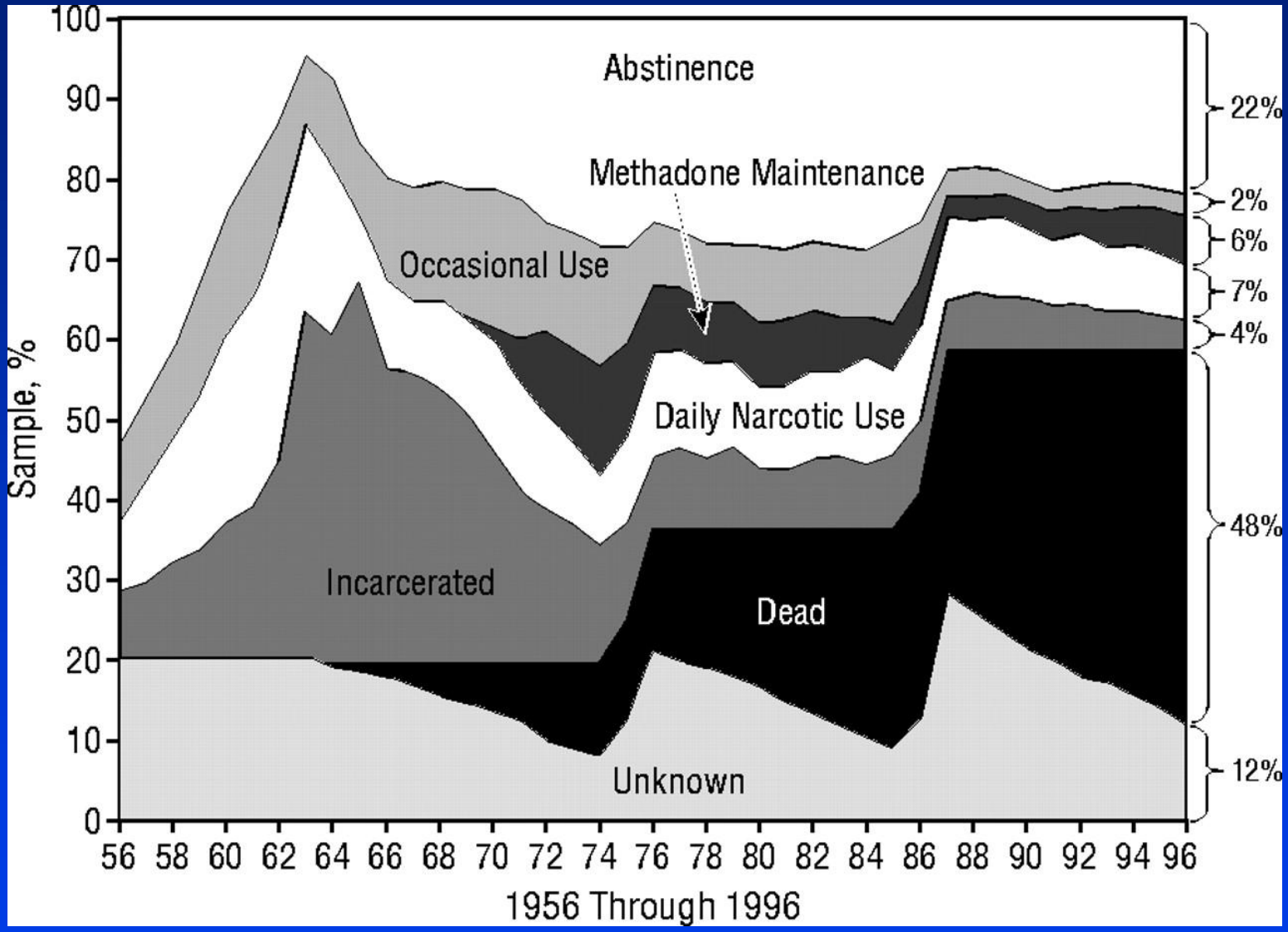
- Use as many effective tools as are available
- One size does not fit all: as many doors as possible
- A full continuum of care: multiple services with flexible responses
- Institutional affiliation promotes engagement
- Expectation of relapsing/remitting course
- Expectation of variable and shifting treatment readiness
- Recovery as a gradual process, not an overnight event -- expectation of incremental progress

Medications for Opioid Addiction

Buprenorphine

Extended Release Naltrexone

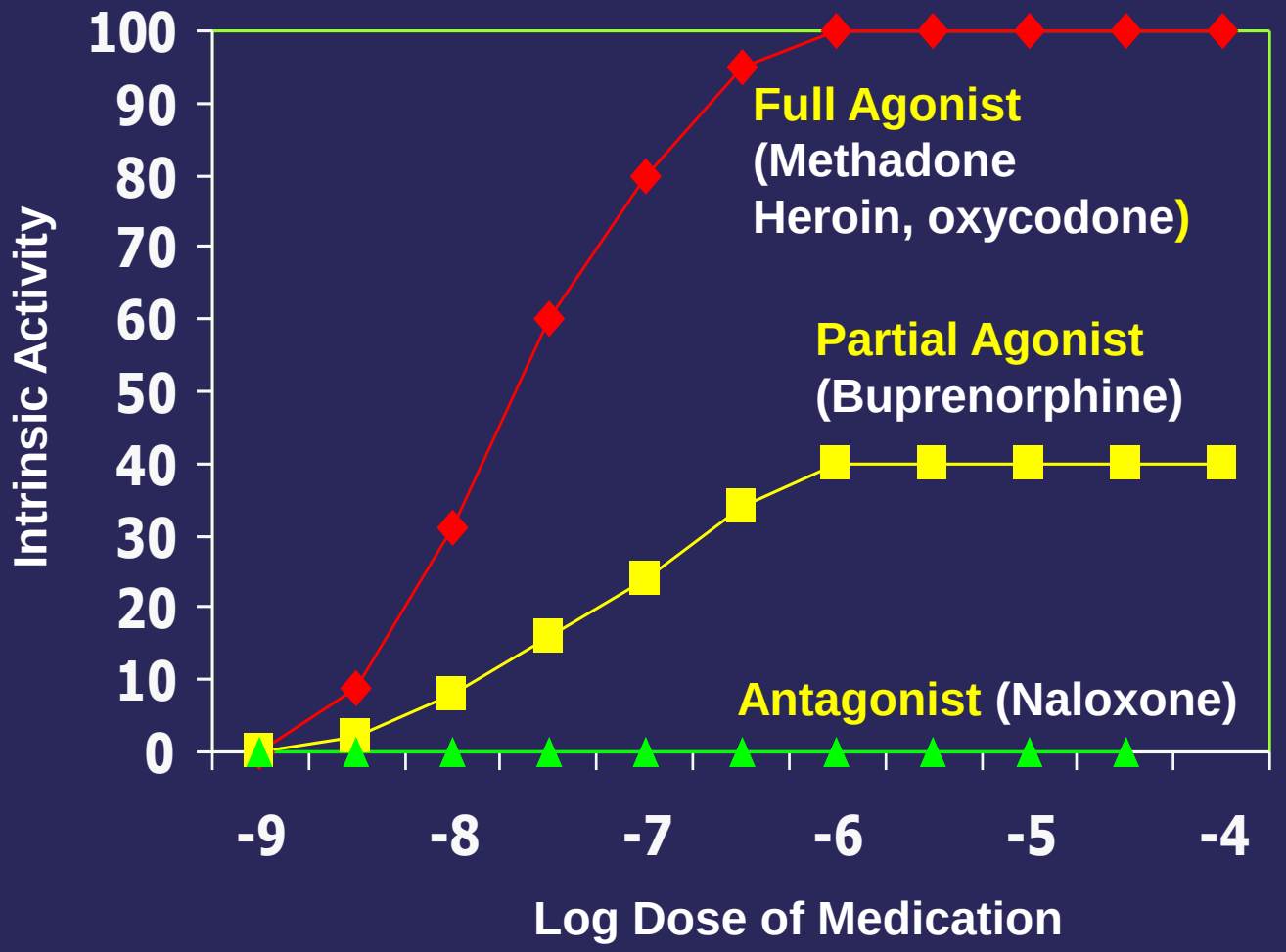
Heroin Addiction History



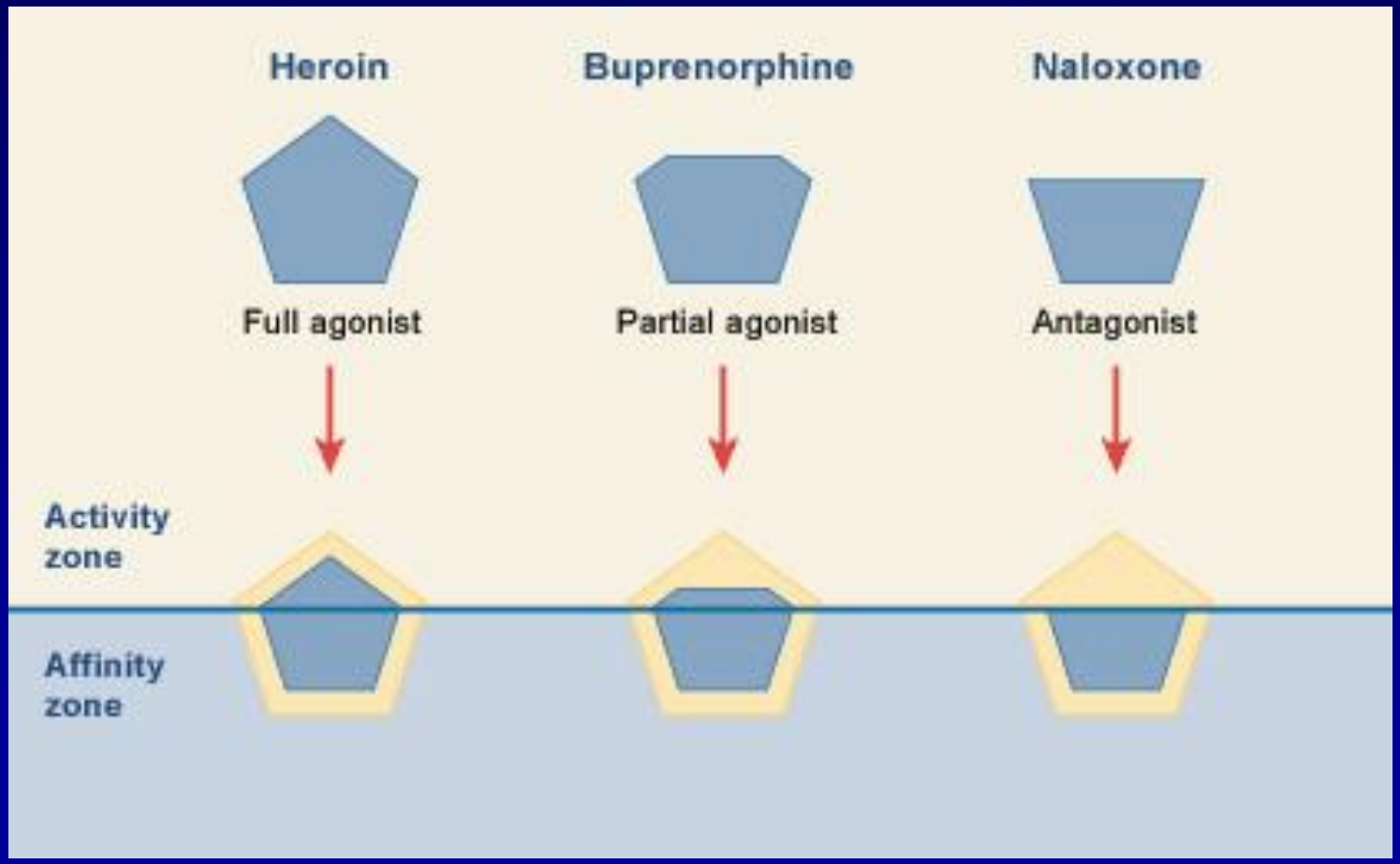
Hser, Y.-I. et al. Arch Gen Psychiatry 2001;58:503-508

ARCHIVES OF GENERAL PSYCHIATRY

Full Agonist, Partial Agonist, and Antagonist of Opioids



Action at the receptor - summary



Some Differences Between Heroin Addiction and Opioid Agonist Treatment

	Heroin Addiction	Opioid Agonist Treatment
Route	Injected	Oral or Sublingual
Onset	Immediate	Slow
Euphoria	Yes	No
Dose	Unknown	Known
Cost	High	Low
Duration	4 hours	24 hours
Legal	No	Yes
Behavior	Chaotic	Normal

DSM-IV Criteria For Substance Dependence

A maladaptive pattern of use leading to clinically significant impairment or distress, manifested by 3 or > of the following in a 12-month period:

1. **T**olerance (increased amounts or diminished effects)
2. **W**ithdrawal (withdrawal syndrome or use to relieve or avoid withdrawal)

(Addictive Behaviors – loss of control)

3. **E**fforts or desire to cut down or control use
4. Taken **L**arger amounts or over a **L**onger period than intended
5. **S**ocial, recreational or occupational activities given up
6. **T**ime spent in activities necessary to obtain the substance
7. Use despite **P**ersistent or recurrent **P**hysical or **P**sychological problems

Forms of buprenorphine

- Suboxone
  - (Buprenorphine / naloxone combination)
- Subutex
  - Mono product
- Buprenex
  - Injectable

Suboxone Administration

- Sub-lingual
- Tabs and strips
  - Strips dissolve faster
  - Strips harder to divert
- Bitter taste
- Sip of water before to moisten mouth; mint afterwards.

Getting started – Medication induction

- Must be in withdrawal for 1st dose
- Supervised vs home induction
- Relatively rapid dose adjustment
- Practical considerations for medication supply
  - Insurance coverage,
  - Prior authorization
  - Co-pays

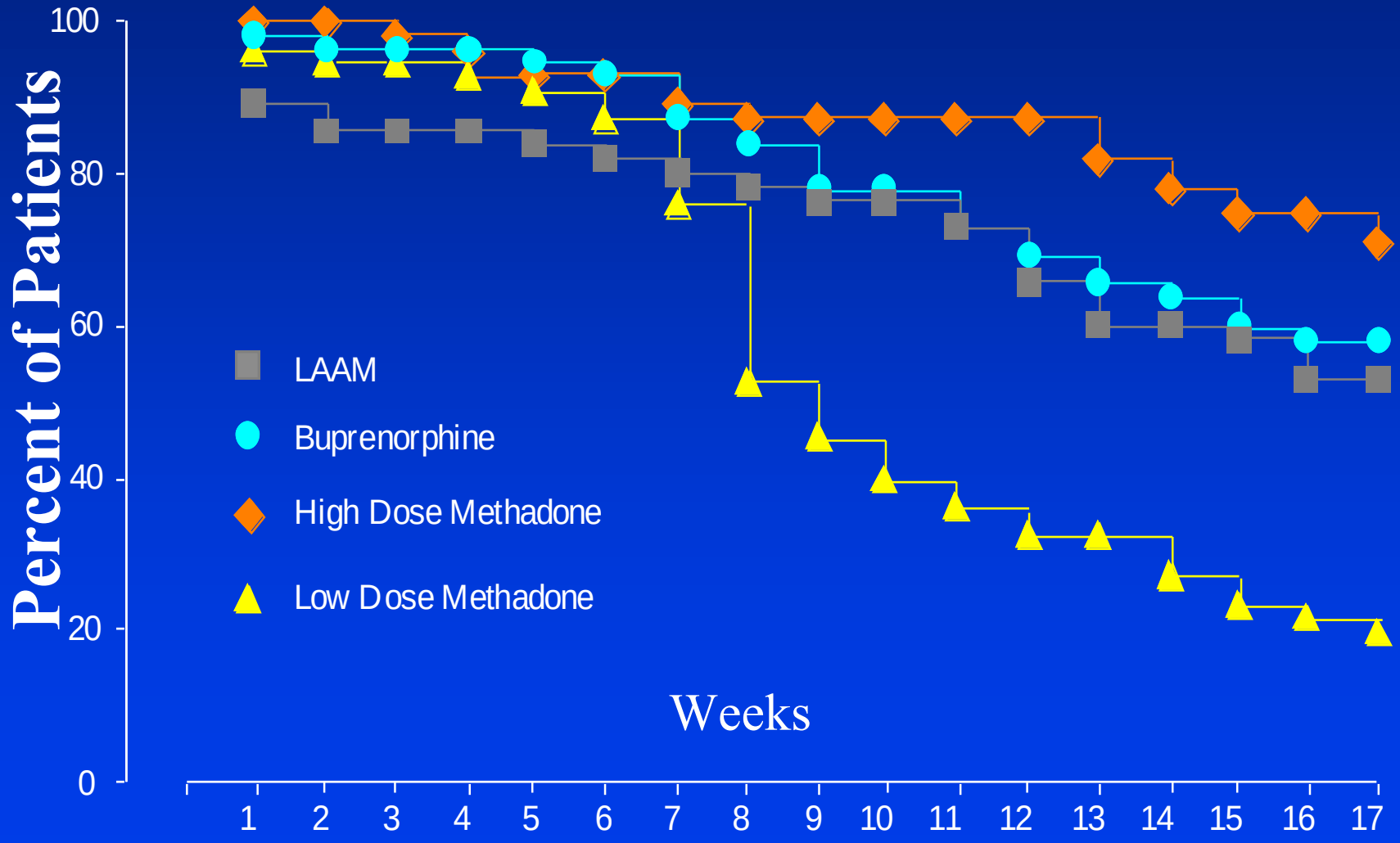
Medications, mischief, and monkey business

- Diversion
- Non-compliance
- Inconsistency
- Other substances

Preventing diversion

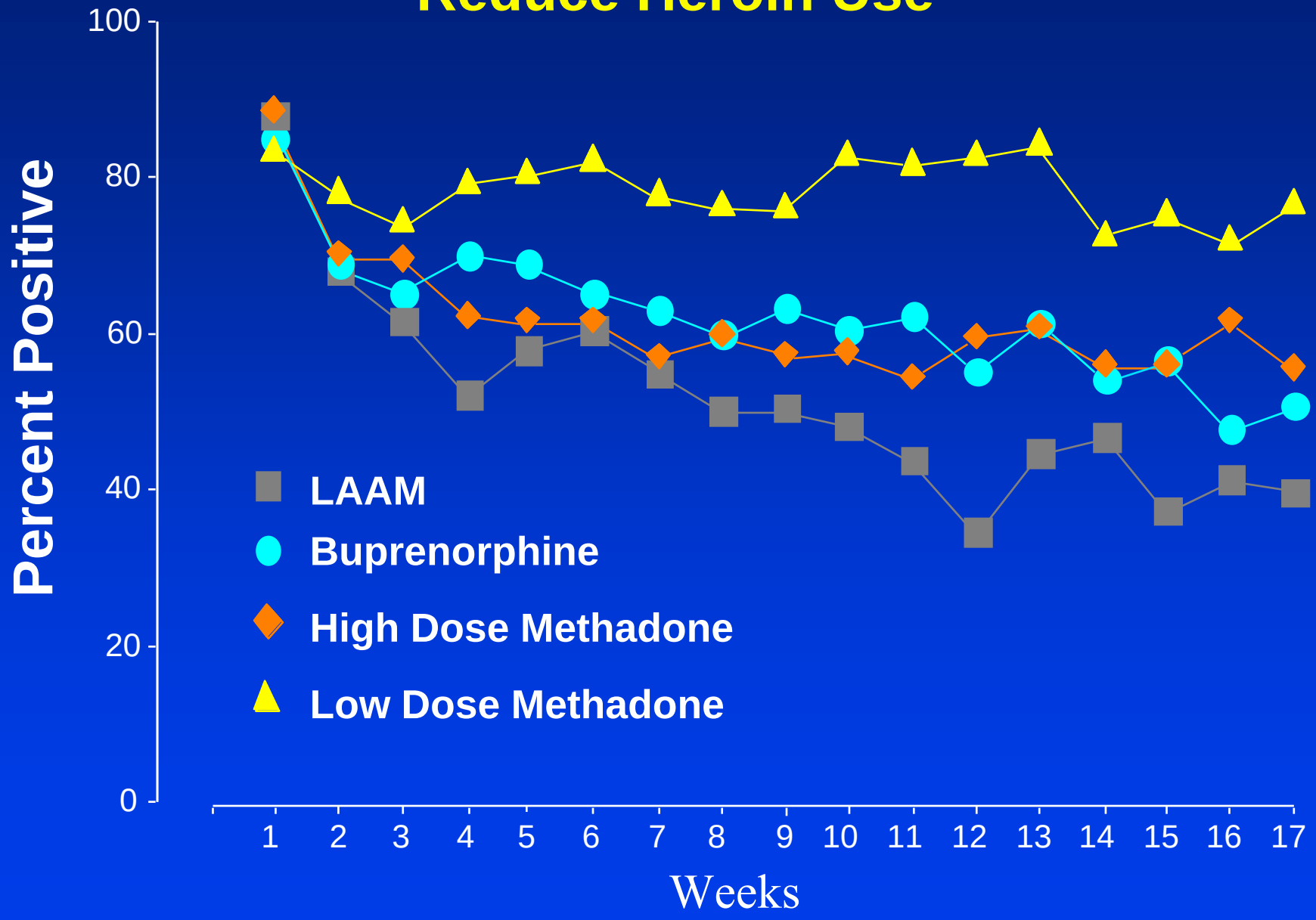
- Start with small supplies
- Limit dose to 24 mg with rare exceptions
- UDS for bupe
- Management of “lost” medication / Rx
- Medication call-backs

Buprenorphine & High Dose Methadone Increase Time in Treatment

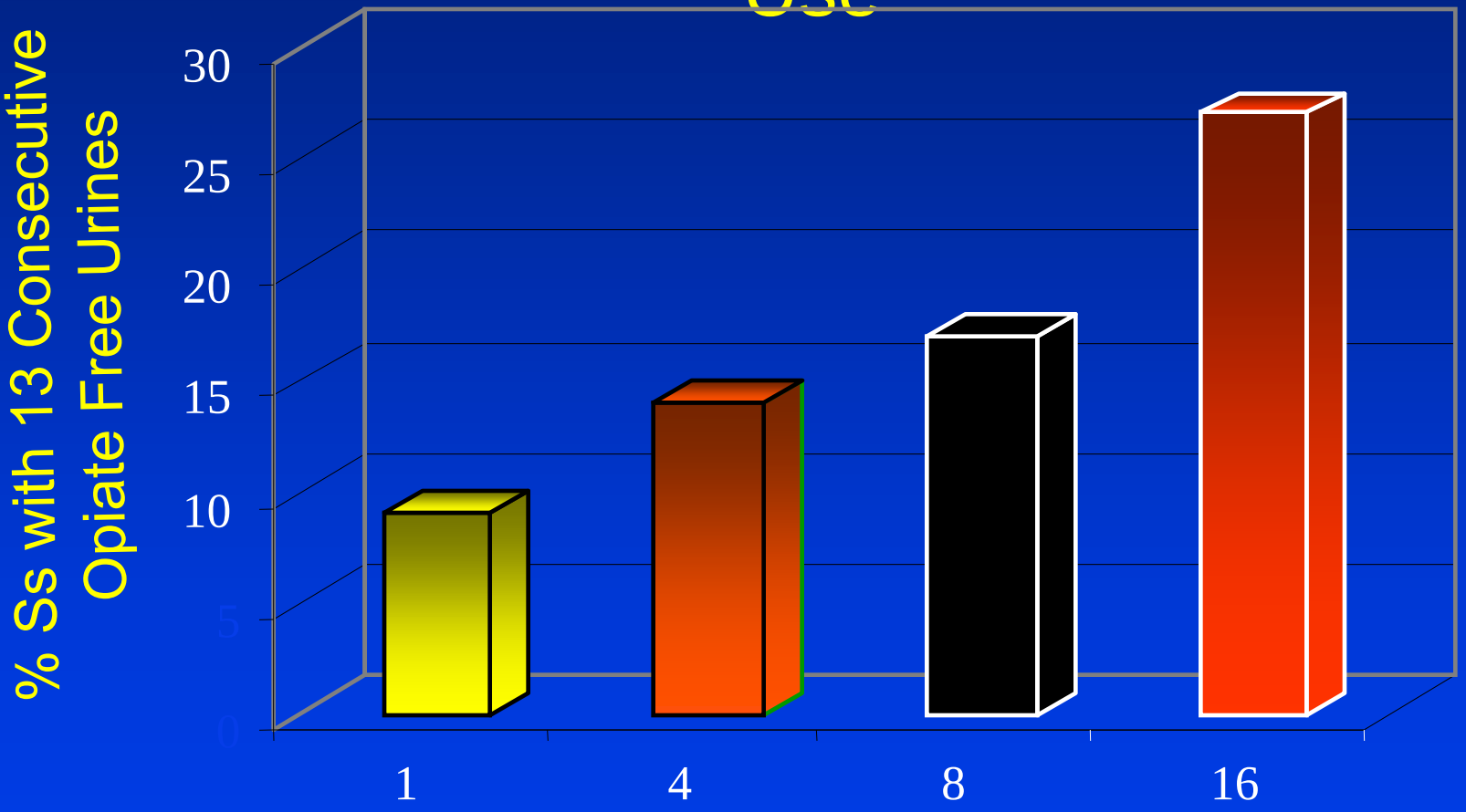


From: Johnson et al., 2000

Buprenorphine & High Dose Methadone Reduce Heroin Use

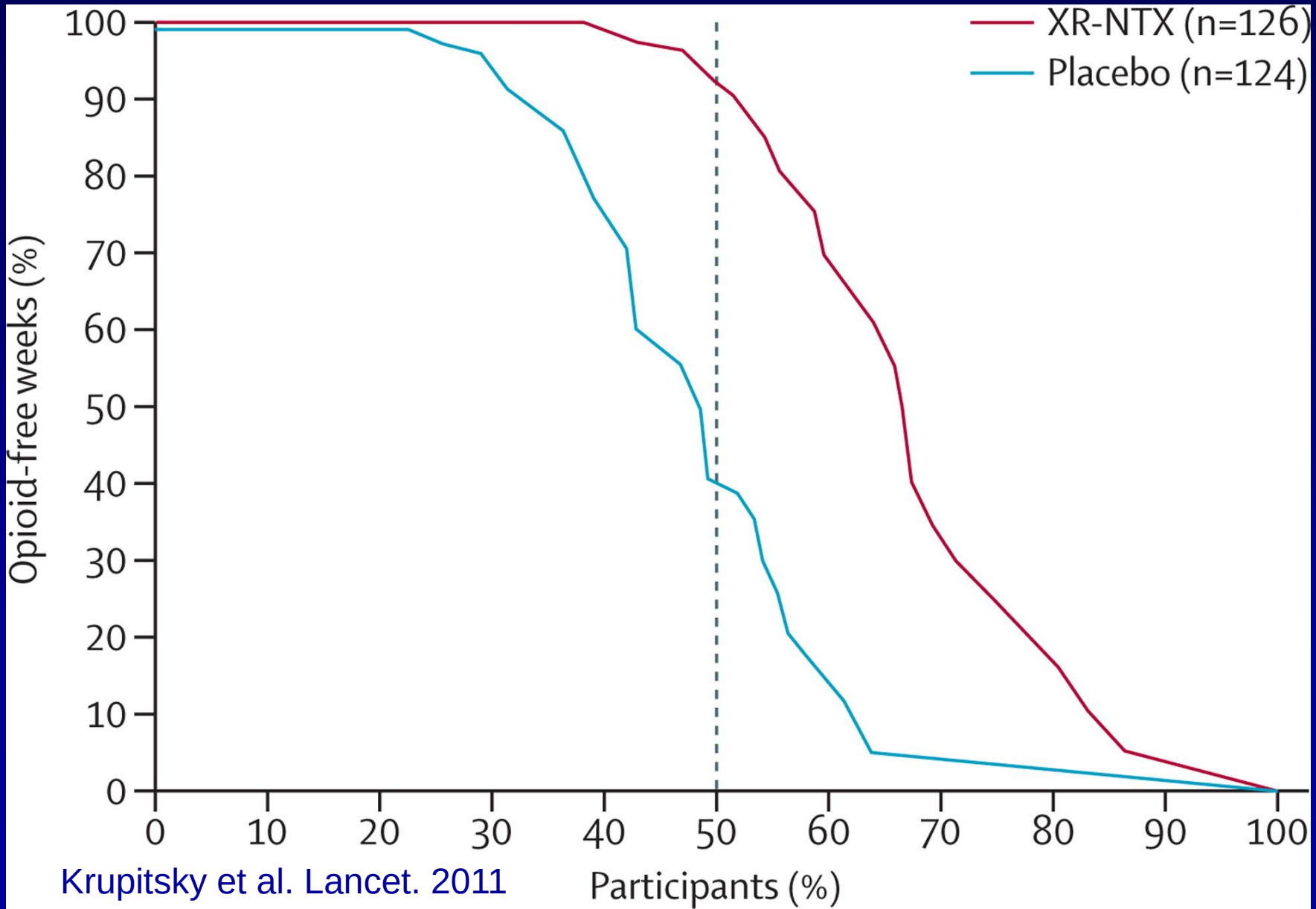


VA Multi-site Study: Buprenorphine's Dose Effect on Opiate Use



Ling et al Addiction 93:475-86, 1998

Percent of confirmed opioid-free weeks (cumulative)



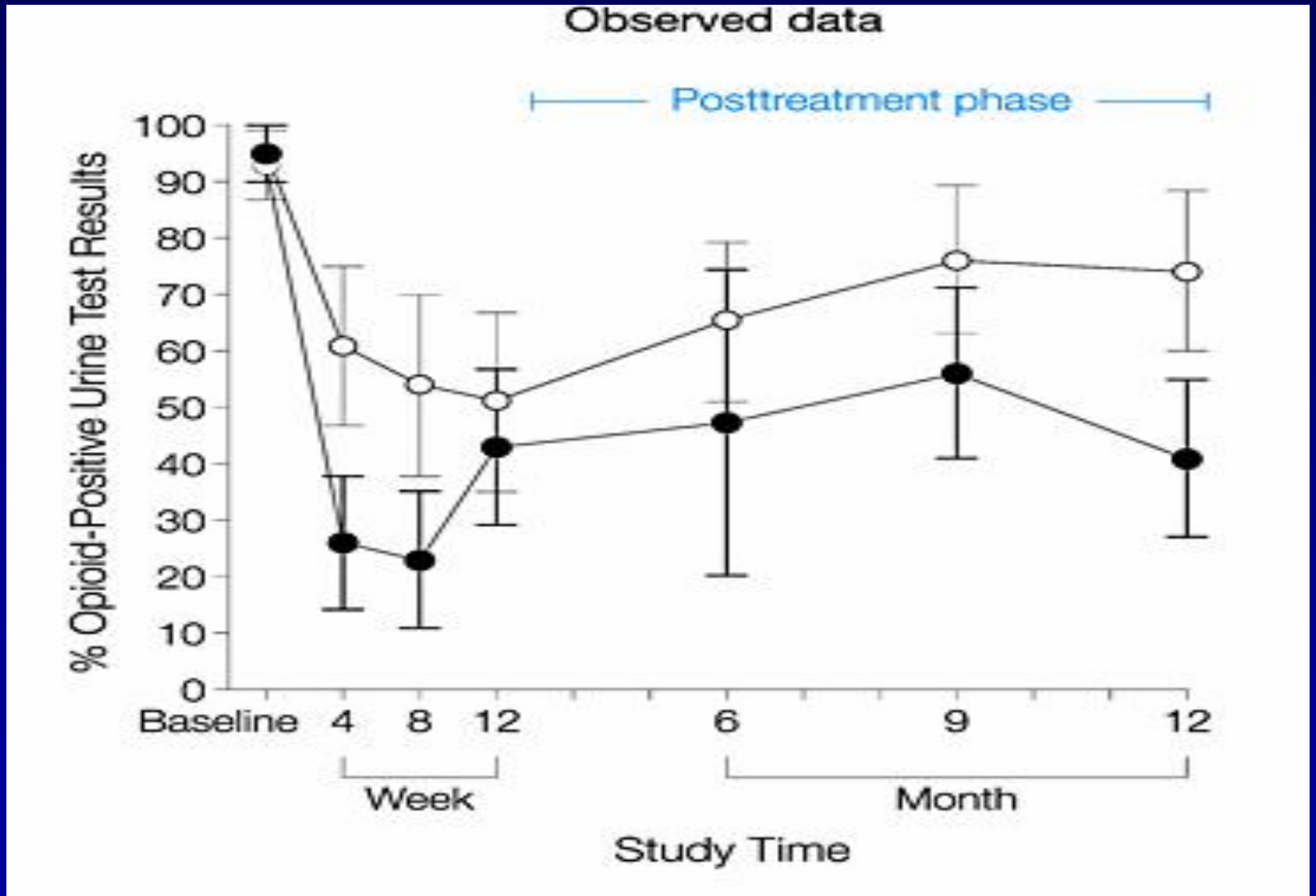
Krupitsky et al. Lancet. 2011

Extended release naltrexone induction

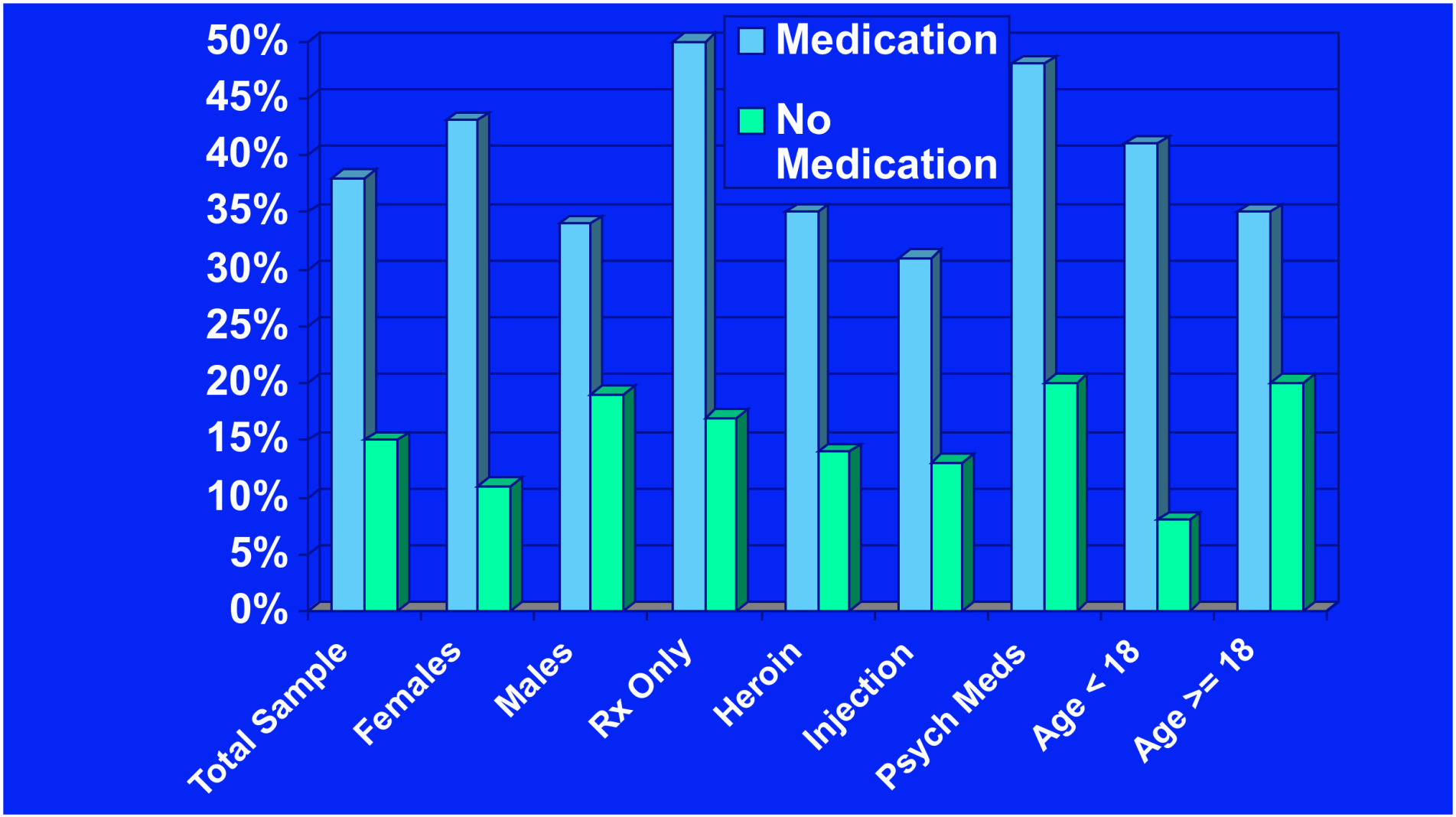
- Detox
- Opioid-free washout period 5-7d
- Test dose(s) oral naltrexone
- XR-NTX injection with observation
- Monthly injections

Opioid Addicted Youth

CTN Youth Buprenorphine Study
Opioid Positive Urines: 12 weeks Bup vs Detox



Retrospective Chart Review in Youth
Medication vs. No Medication
Cross-sectional retention at 26 weeks



Medications for Alcohol Dependence

Naltrexone

Extended release naltrexone

Acamprosate

Disulfiram

Topiramate

Primary Pharmacotherapies for Alcohol Dependence

*Approved by the FDA **(for alcohol dependence)** :*

- Disulfiram *1951*
- Naltrexone *1994*
- Acamprosate *2004*
- Long-acting injectable naltrexone *2006*

Off-Label

- Topiramate

Disulfiram (Antabuse)

- Mechanism: aversive operant conditioning
  - Blocks aldehyde dehydrogenase enzyme
  - Cause build up of toxic metabolite acetaldehyde
  - Flushing, nausea, headache, seizures, death
- Infrequent use
- Effectiveness limited by poor compliance (<20%)
- Effectiveness improved with special compliance procedures

Acamprosate (Campral)

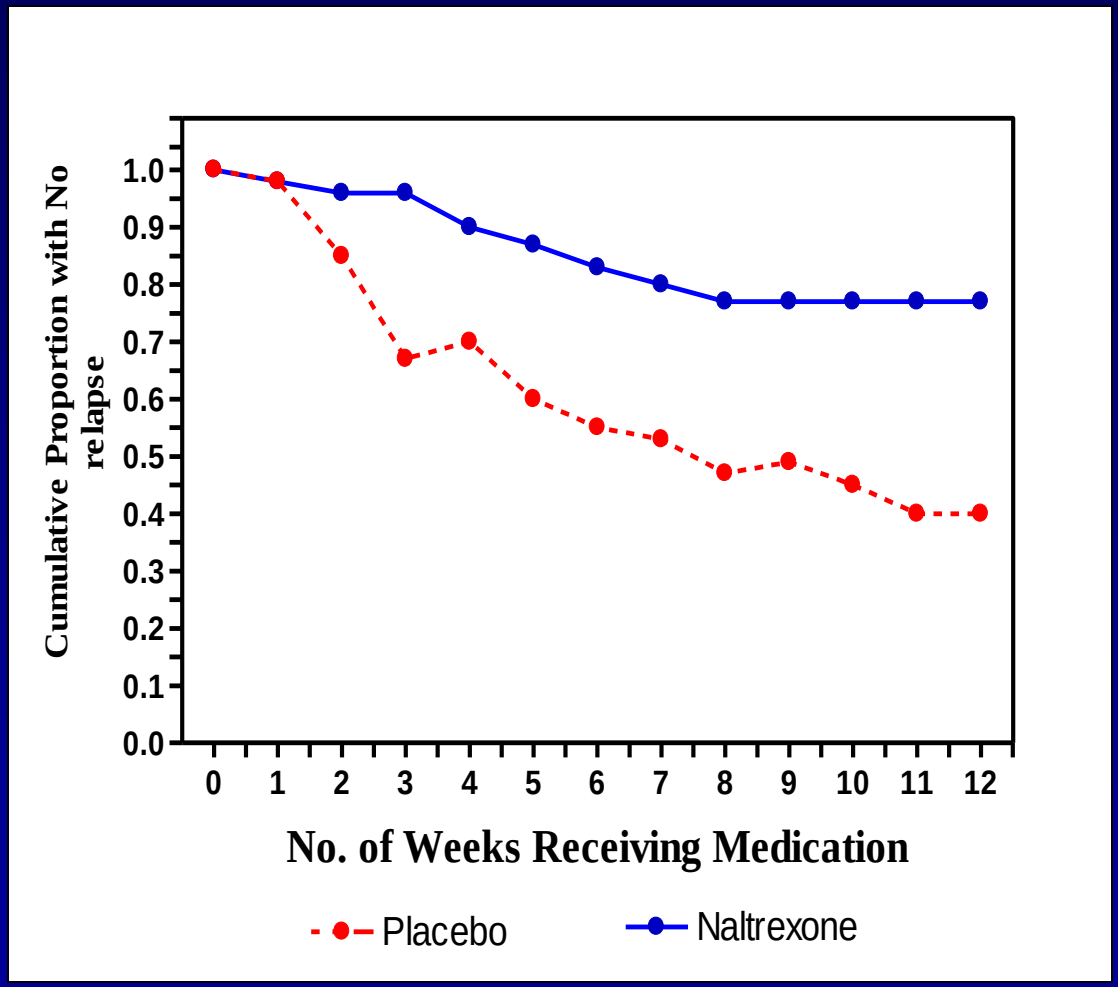
- Mechanism: boosts GABA, blocks glutamate, modulates subacute withdrawal
- Initiated after abstinence (≥5d)
- Increases abstinence, time to first drink, days abstinent
- Major benefit of motivation for abstinence
- Routine dosing: 666 mg (2 x 333mg pills) three times/d, difficult to sustain adherence
- Side effects: diarrhea
- Years of widespread use in Europe

Naltrexone (ReVia)

- Mechanism: Blocks built-in opioid reward system, decreases reinforcement, decreases craving and pleasure
- Lead-in abstinence improves outcomes
- Does not require motivation for abstinence
- Reduces drinking days, heavy drinking days, relapse to heavy drinking
- Routine dosing: 50-150 mg daily
- Side effects: fatigue; dizziness; appetite suppression, nausea; caution re liver inflammation

Naltrexone

- Reduces relapse, especially when considered as heavy drinking
- Increased response in those with + family history
- Emerging info on genetic markers



Volpolicelli et al. 1992

Naltrexone vs Acamprosate

- Naltrexone perhaps more active on the positive reinforcement side, during active use phase
- Acamprosate perhaps more active on the negative reinforcement side, during subacute withdrawal phase
- Combination therapy?
- Bottom line : both effective, should be used routinely, effect sizes in the same range as our best psychosocial treatments

Depot Naltrexone (Vivitrol)

- Monthly injection (380 mg)
- Addresses problems with adherence / complaince
- Initial results comparable, probably better, than oral
- Hope for big market penetration, broad acceptance and paradigm shift
- (Additional use for opioids)

Topiramate (Topamax)

- Main uses: seizures, migraines
- Routine dosing: 100-300 mg/d, twice daily dosing
- Mechanism: boosts GABA, blocks glutamate
- Side effects: changes in sensations and taste, decreased appetite, concentration problems
- Abstinence not required

XR-NTX in the real world

- XR-NTX for alcohol, 3 month open label in primary care with brief MD delivered counseling (n =72)

# injections	1 injection	2 injections	3 injections
% received	90%	68%	56%

Drinking Outcomes	Baseline	3 months
Median drinks /d, subjects receiving all 3 doses	4.1	0.4
Median drinks /d, all subjects	5.4	3.4
Median % drinking days, subjects receiving all 3 doses	0.6	0.1
Median % drinking days, all subjects	0.6	0.5
Median % heavy drinking days, subjects receiving all 3 doses	0.6	0.1
Median % heavy drinking days, all subjects	0.6	0.3

- No association with pre-treatment lead-in abstinence
- AA attendance and IOP attendance very highly associated with medication retention

Lee J et al. Extended release naltrexone for treatment of alcohol dependence in primary care. *JSAT*. In press

Healthcare utilization impact of Etoh meds

- Large commercial insurance claims database, comparison of 6 months pre and 6 month post, n=2977 who filled any anti-alcohol Rx vs case matched controls
- Use of Rx associated with reductions in :
  - % with detox admission (8.7% vs 13.4%)
  - % with alcohol-related inpatient admission (6.8% vs 11.2%)
  - Inpatient detox days /1000 pts (706 vs 1163)
  - Alcohol-related inpatient days/1000 pts (650 vs 1086)
  - Alcohol related ED visits/1000 pts (121 vs 171)
  - Detox costs /1000 pts ($1.9M vs $3.1M)
  - Alcohol-related inpatient costs ($1.8M vs $3.0M)

Mark et al. Am J Managed Care. 2010.

Medications for Nicotine Dependence

Nicotine replacement therapy

Bupropion

Varenacline

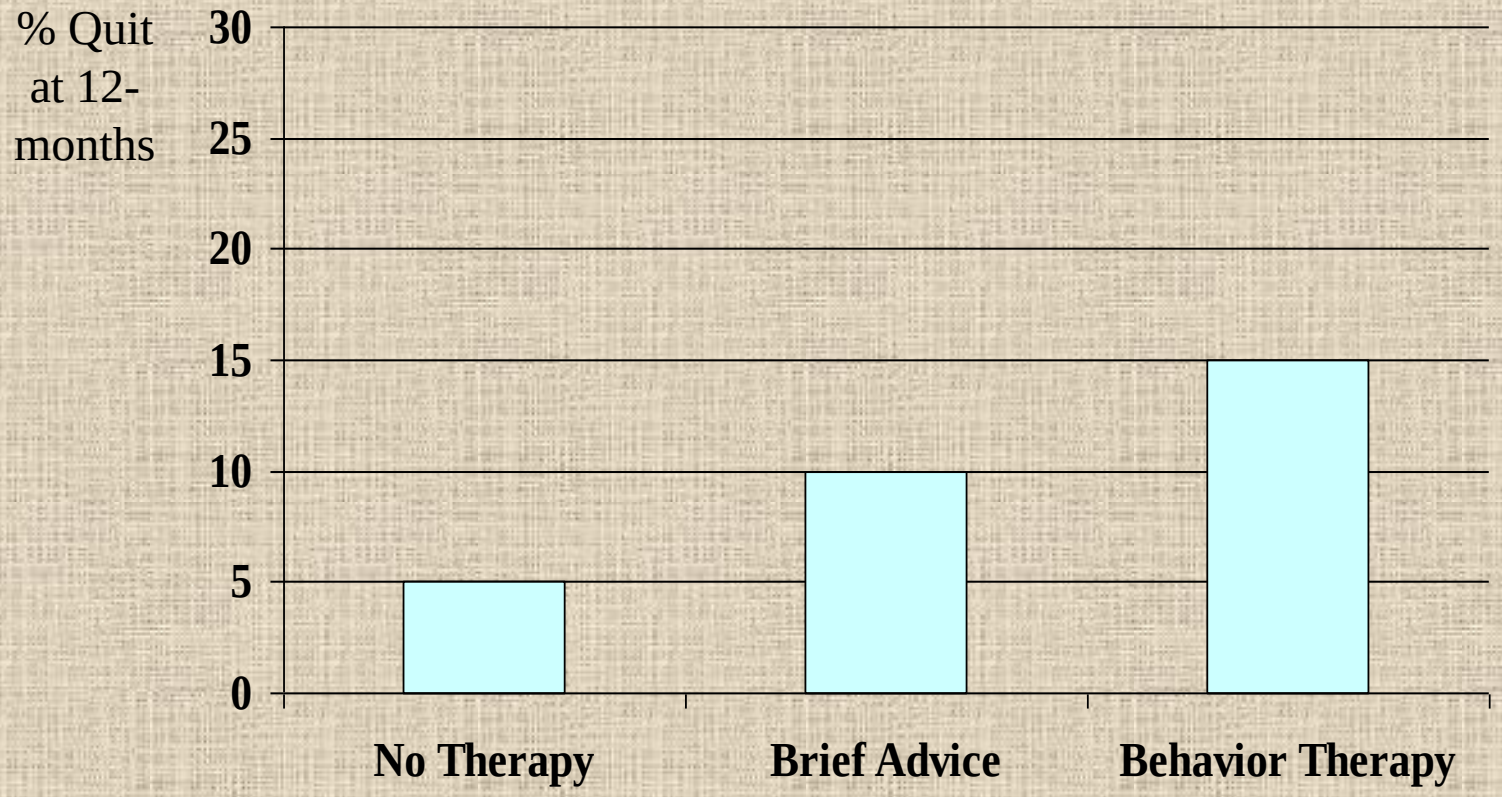
Nicotine Addiction Medications

- **"Smoking is the leading preventable cause of disease and death in the United States"**
  - **–440,000 premature deaths per year**
  - **–Cost to the nation, $157 billion dollars**

Report of Surgeon General on the Health Effects of Smoking, 2004

Current treatments

Effectiveness of Non-Pharmacologic Treatments



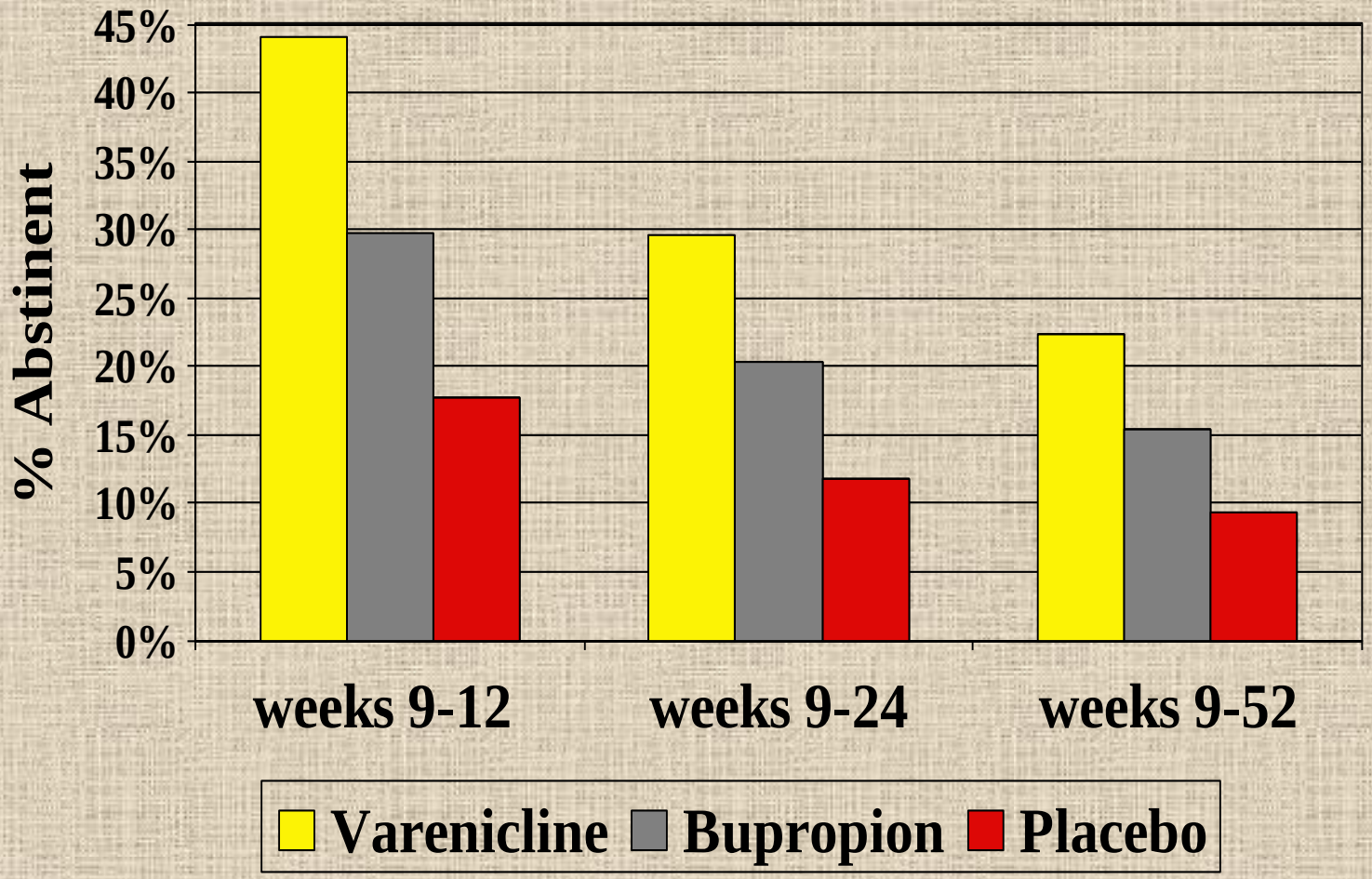
Lerman, Patterson, & Berrittini, 2005.

Nicotine replacement therapy (NRT)

- Patches
- Gum
- Nasal spray
- E-cigarettes

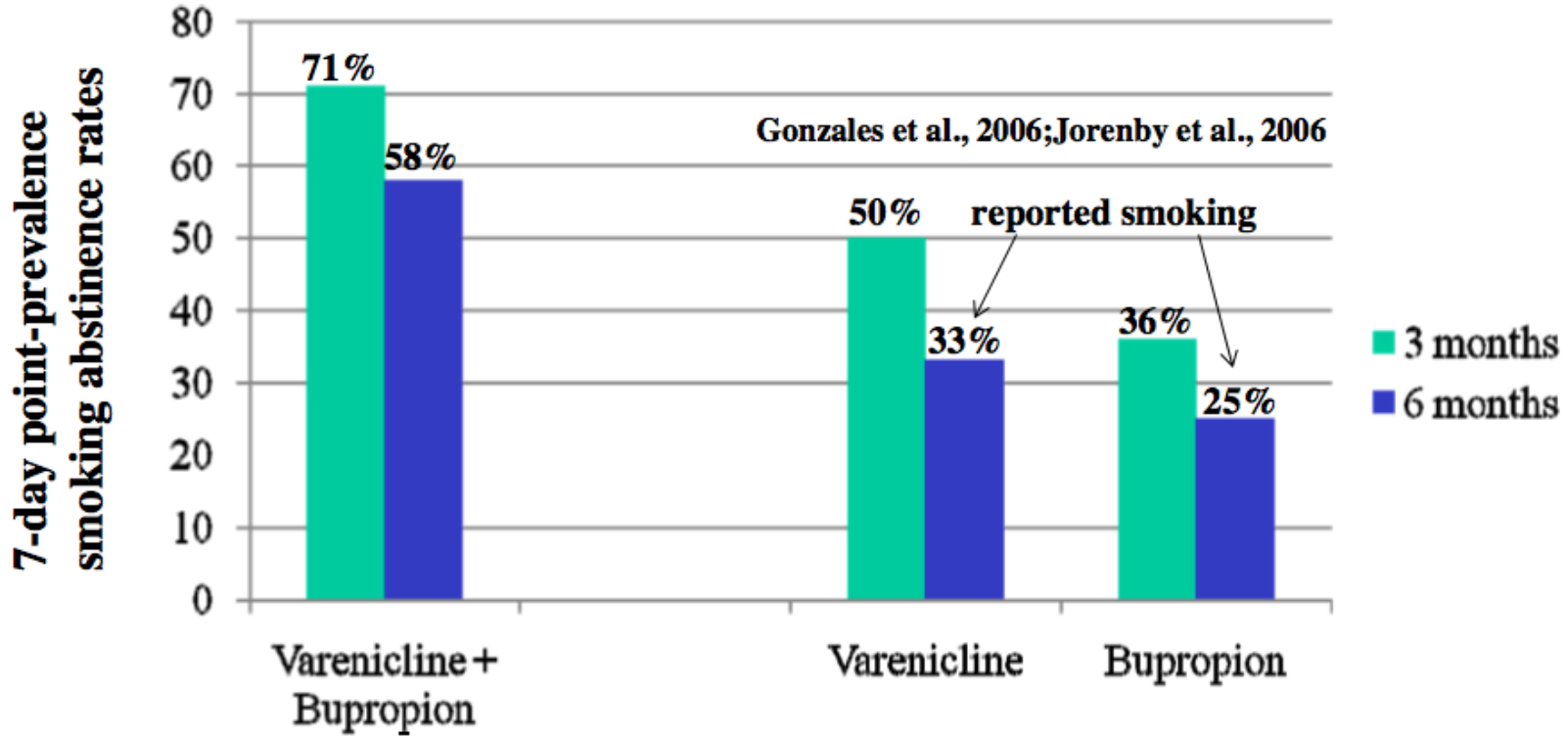
Nicotine – current (but under-utilized) treatments

Abstinence Rates Varenicline vs. Bupropion vs. Placebo



Nides et al. Am J Health Behav 32: 664-675, 2008

Varenicline & Bupropion SR Combination Therapy for Smoking Cessation



Ebbert JO et al. Nic Tobacco Research 2009;11(3):234-239.

A speculative partial catalog of the future

New uses for existing meds

- XR-Naltrexone for opioids
- Vigabatrin for cocaine
- XR-Naltrexone for stimulants
- Pregabalin for benzos
- Disulfiram for cocaine
- Buspirone for stimulants

New meds

- Cocaine vaccine
- Implant naltrexone
- Implant buprenorphine
- Cannabinoid antagonists
- NK-1 antagonists for stress-induced relapse
- Metabolic enzymes

We've come a long way

Clinical Implementation Issues

Why medication? Can you be in recovery on medicines

- Medicines just a crutch or band-aid
  - Maybe. Like meetings or groups.
- If the patients like it so much, there must be something wrong.
  - But if they don't like it, it doesn't matter how good it is.
- If medications are an "easy fix" will patients refuse needed psychosocial treatments and supports.
  - Actually, they come to psychosocial treatment *more*.

Why medication? Can you be in recovery on medicines

- If medications eliminate cravings will patients miss opportunity for needed cravings management?
  - Academic if they relapse. Postpone until later when stronger. Open question - maybe need later high intensity counseling.
- Abuse and diversion
  - Real issue, needs to be managed, but not as problematic as scare stories make it out to be.

Pharmacological Treatment

- Question:
  - Which is better - medications or counseling?
- Answer:
  - Yes

Barriers to effectiveness and adoption

- Cost
- Knowledge and training
- Prejudice and misunderstanding
- Lack of medical involvement in treatment
- Lack of delivery system models
- Limited potency of medications
- Side effects
- Problems with adherence and compliance

What do we do with this patient?

- 36 M injection heroin
- 4 episodes residential tx (2 AMA, 1 completed), 3 episodes outpatient treatment
- Longest abstinence 6 months while incarcerated, 4 months while in recovery house, 2 months while in IOP
- Previous suboxone treatment (monthly supply Rx x 4), took erratically, sold half
- Now intermittently buying street suboxone
- Presents in crisis seeking treatment (“Can I have my meds now, I’m kind of in a rush...”)

What do the patients want?

- Sobriety? Recovery? Abstinence? Spiritual enlightenment?
- A little less heroin in my life?
- Crisis relief
- Why now?

Meet the patients where they are?

- “I’d like a month’s supply of suboxone please”
- “Sure I’ll come to group occasionally when I can make it”
- “I agree I’ve been using too much heroin but cocaine is not a big problem for me”
- “Why can’t I take xanax for my anxiety. Nothing else works…”

Is everything on the menu?

"And if you like comfort food, I would recommend the Xanax stuffed pork-loin."

Practical Treatment Approaches

- 95% is just showing up

Standard Compliance Enhancement Procedures

- Role induction and explicit unified expectation: the earlier in the treatment process this role is induced, the more likely the patient may be to develop a “routine” for taking the medication
- Compliance monitoring by the health care team, including explicit inquiries using non-judgemental questions in order to obtain an accurate medication-taking history
- Encouragement and monitoring by the counselor or therapist
- Coordination and collaboration between medical and counseling staff around medication monitoring

Additional adherence enhancement

- Long acting formulations
- Increased intensity and frequency of provider monitoring
- Increased coordination and communication between medical and counsleing staff
- Role of concerned other in monitoring of adherence (eg network therapy)
- Supervision of (self-) administration by caregiver or staff or peers
- Direct staff administration

Medication Treatment Collaborative Team Approach

- Illness education and role induction
- Family (or other support network) involvement and commitment
- Cross discipline monitoring
  - Presence of symptoms
  - Medication compliance
  - Treatment response
  - Side effects
  - Social influences
- Expectations and arrangements for continuing care

Individualized treatment

- Choice of medication
- Duration of medication
- Treatment intensity
- Group vs individual
- Family involvement
- Response to continued use
  - Primary target substance
  - Other substances

Other substances

- Cocaine / methamphetamine
- Benzodiazepines
- Alcohol (when not the primary treatment target)
- MJ (esp in youth)
- others

Tools for individualized treatment

- Access to medication as a motivational incentive
  - Access to prescriptions vs daily administration
  - Increased duration of Rx
  - Point of delivery and timing of Rx

Tools for individualized treatment

- Dose of counseling as motivational incentive
  - Decreased frequency
  - Flexibility
  - Ask for patient's plan as a starting point

Special problems
Insomnia

- Very common
- Easy to treat with non-habit forming medications
- Easy early reinforcement of treatment participation through symptom relief

Special problems
Depression

- Very common
- Very responsive to treatment with medications
- To wait or not to wait?

Special problems
Anxiety

- “I’ve tried everything and nothing works except xanax”
- A symptom not a disease
- Characteristic side effect profile of benzos including rebound anxiety
- Suignificant safety concerns with bupe
- Immediate relief vs lasting relief
- SSRI + CBT usually most effective, but takes time
- Desensitization and self-soothing

Special problems
Pain

- Very complicated
- Suboxone surprisingly helpful early on
- But like all opioids limited sustained benefit over the long run
- Most important intervention is clarification of treatment goals: function over comfort
- Good response to non-opioid pain meds

What's the right balance?

- Stricter, more uniform requirements for continuation favors action stage, endorses and reinforces success, leads to greater rates of success in those that remain, increased atmosphere of "real recovery" but leaves many behind
- More flexible approaches favor contemplation stage, allow gradual engagement and incremental success, broader inclusion, increased atmosphere of "gas 'n go" but captures many in contemplative stage
- Finding a balance with motivational incentive approach with access to medication as the contingency

A sprint or a marathon?

Early: I agree I was out of control with the dope, but I can still use a little oxy on the weekends.

Middle: I'm a heroin addict, not an alcoholic. I just need to stop using heroin. A few beers is fine.

Later: When I get drunk, I end up using heroin again. Maybe I need to stop drinking too. But taking a little xanax when I'm stressed is no big deal.

(sigh)