Overview: Opioid Dependence Treatment with Buprenorphine/ Naloxone

U.S. Legislation Enabling Office-Based Treatment of Opioid Dependence

- Drug Addiction Treatment Act of 2000: "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment" (H.R. 4365, Children's Health Act of 2000)

Amended Controlled Substances Act: DATA 2000

- Revision in legislation allows a physician to prescribe narcotic drugs in schedules III, IV, V, or combinations of such drugs, for the treatment of opioid dependence
- Drugs and practitioners must meet certain requirements

Amended Controlled Substances Act: DATA 2000

- Narcotic drug requirements:
  - Approved by the US FDA for use in maintenance or detoxification treatment of opioid dependence
  - Schedule III, IV, or V
  - Drugs or combinations of drugs

Amended Controlled Substances Act: DATA 2000

- Practitioner requirements:
  - "Qualifying physician"
  - Has capacity to refer patients for appropriate counseling and ancillary services

Amended Controlled Substances Act: DATA 2000

- Practitioner requirements:
  - No more than 30 patients (individual); now increased to 100 patients per practitioner, but those who undertake the higher patient number can only do so at least one year after having submitted the waiver and must notify CSAT of their intent to do so (December 2006)
  - No limit for group practices (August 2005)
  - Must register with SAMHSA and DEA

Amended Controlled Substances Act

- "Qualifying physician":
  - A licensed physician who meets one or more of the following:
    1. ABPN Added Qualification in Addiction Psychiatry
    2. Certified in Addiction Medicine by ASAM
    3. Certified in Addiction Medicine by AOA
    4. Investigator in buprenorphine clinical trials

Amended Controlled Substances Act

- "Qualifying physician" (continued):
  - Meets one or more of the following:
    5. Has completed 8 hours training provided by AAAP, AMA, AOA, APA, ASAM (or other organizations which may be designated by HHS)
    6. Training/experience as determined by state medical licensing board
    7. Other criteria established through regulation by the Secretary of Health and Human Services

Amended Controlled Substances Act

- Practitioner requirements:
  - "Qualifying physician"
  - Has capacity to refer patients for appropriate counseling and ancillary services
  - Psychosocial interventions *in addition* to medication treatment are the standard of care for treatment of opioid dependence

Amended Controlled Substances Act: DATA 2000

- State legislation:
  - A state may not preclude a practitioner from dispensing or prescribing buprenorphine for opioid dependence treatment unless the state enacts a law prohibiting the practitioner from doing so

Amended Controlled Substances Act: DATA 2000

- Evaluation period:
  - During the first three years, DHHS and DEA evaluated safety and efficacy
  - Safety includes protection of the public health against diversion of the drug

Amended Controlled Substances Act: DATA 2000

- DHHS has evaluated:
  - Whether the treatment is effective in the office setting
  - Whether access to treatment has been increased
  - Whether there have been adverse consequences for the public health

Amended Controlled Substances Act: DATA 2000

- DEA has evaluated:
  - Extent of violations of the 30 patient limit
  - Extent of diversion of the medication
  - Physician record keeping and security measures related to on-site medication storage
  - DEA will continue to visit two prescribers in each DEA district every 18 months

Amended Controlled Substances Act: DATA 2000

- Evaluation period:
  - On the basis of these evaluations, DHHS and DEA have decided the law should remain in effect
  - Office-based treatment of opioid dependence will continue as a treatment option for patients who need it
  - Number of providers offering this treatment will continue to grow as the treatment modality becomes more familiar to clinicians and patients

Buprenorphine

- Opioid partial agonist
- Schedule III (vs. methadone: Schedule II)
- Treatment modalities for buprenorphine:
  - Office based treatment
    - Primary Care
    - Specialty (e.g.: Infectious Disease, GI, Psychiatry)
    - Substance abuse treatment clinics
  - Methadone maintenance programs

How Does Buprenorphine Work?

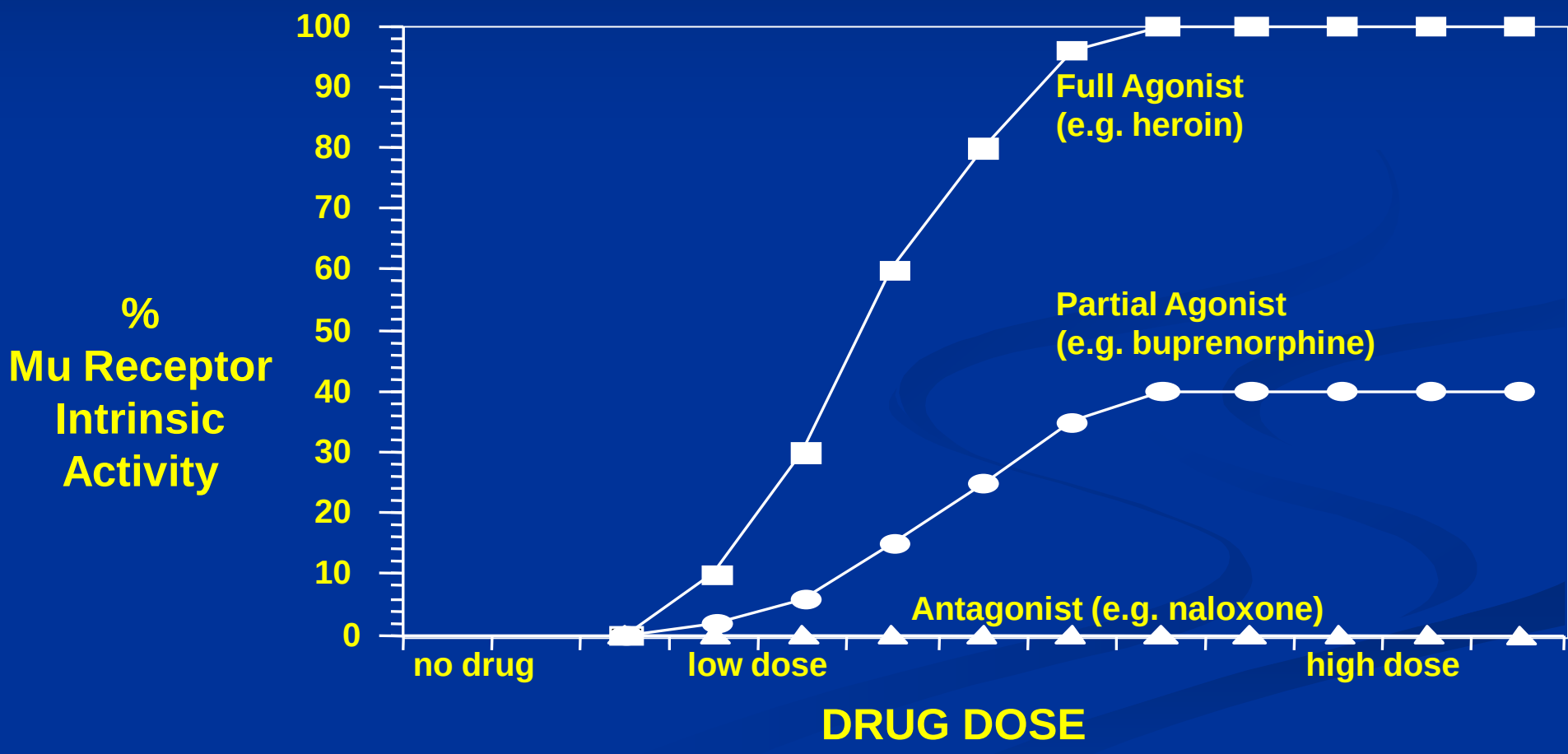
- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine's affinity is strong; it will displace full agonists like heroin and methadone
  - Receptor binding strength (strong or weak), is NOT the same as receptor activation

How Does Buprenorphine Work?

- DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine's dissociation is slow

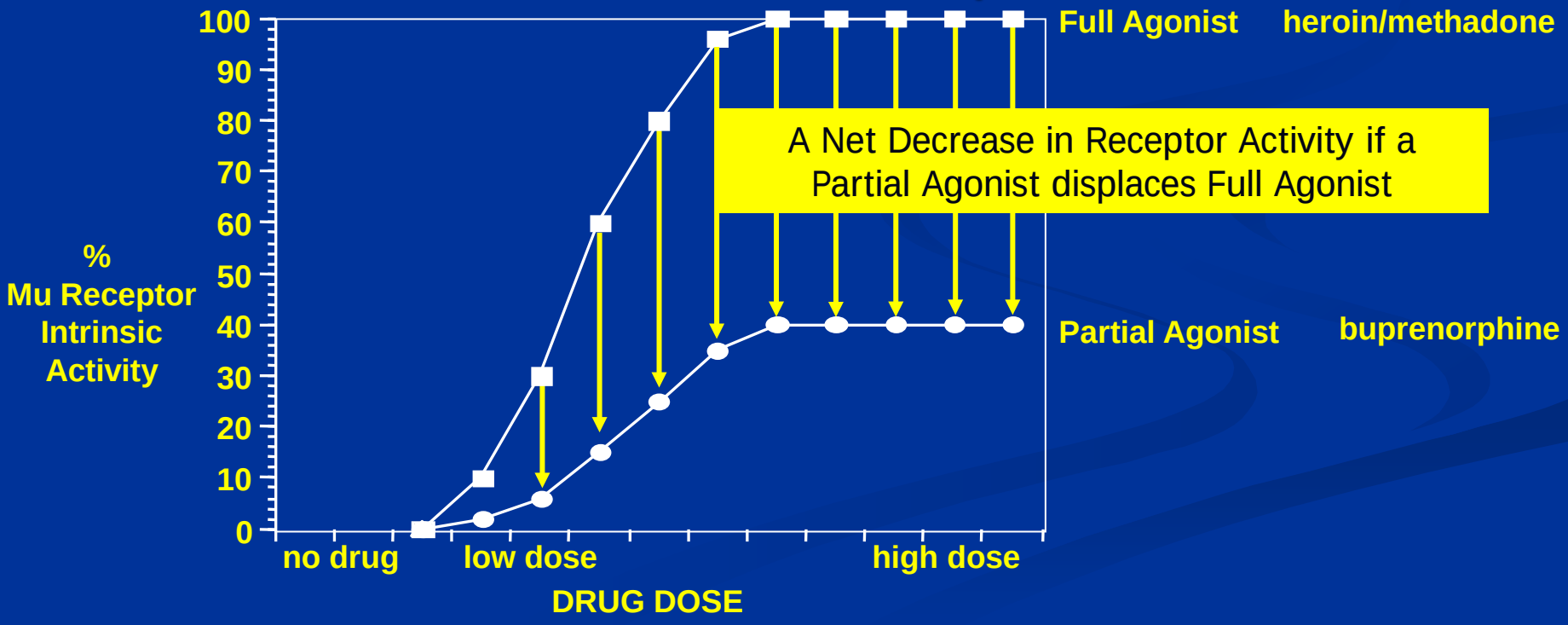
  - Therefore buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding

Buprenorphine is a Partial Agonist



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



Clinical Forms of Buprenorphine

- Parenteral form for treatment of moderate to severe pain (not approved for opioid dependence treatment)
- 7-day Patch (5, 10, and 20 µg/hour) for severe pain
  - Sublingual forms not approved for pain management
  - Implant now in clinical trials for treatment of opioid addiction

Clinical Forms of Buprenorphine

- Sublingual tablet form for treatment of opioid dependence
  - "Combo" buprenorphine/naloxone
    - Bup 2mg/Nlx 0.5mg or Bup 8mg/Nlx 2mg
    - Developed to decrease diversion to i.v. use
    - Preferred form for treatment
    - Precipitated withdrawal if injected by opioid dependent person
  - "Mono" sublingual form = buprenorphine
    - Bup 2mg or Bup 8 mg
    - Use in pregnancy

Clinical Forms of Buprenorphine

- Buprenorphine/naloxone strip (FDA approved 8/31/10)
- Equivalent in strength to tablets
- Dissolves more rapidly than tablets
- Participants in clinical trials preferred taste over that of tablets
- Childproof foil packet improves safety of product

Diversion and Misuse

Four possible groups that might attempt to divert and abuse buprenorphine/naloxone parenterally:

1. Persons physically dependent on illicit opioids
2. Persons on prescribed opioids (e.g., methadone)
3. Persons maintained on buprenorphine/naloxone
4. Persons abusing, but not physically dependent on opioids

Diversion and Parenteral Misuse

- Persons physically dependent on short-acting opioids like heroin or pain meds (prescribed or illicit)
- If have short-acting full agonist on receptors
  - then injection of buprenorphine/naloxone will precipitate opioid withdrawal syndrome
- If no short-acting full agonist on receptors
  - by definition will already be experiencing some level of opioid withdrawal syndrome
  - then injection of buprenorphine/naloxone will provide withdrawal relief and give agonist effects

Diversion and Parenteral Misuse

Persons physically dependent on long-acting opioids like methadone (prescribed or illicit)

- If have long-acting full agonist on receptors
  - then injection of buprenorphine/naloxone will precipitate opioid withdrawal syndrome
- If no long-acting full agonist on receptors
  - by definition will already be experiencing some level of opioid withdrawal syndrome, but will take days before it happens
  - then injection of buprenorphine/naloxone provides withdrawal relief; gives agonist effects

Diversion and Parenteral Misuse

Persons physically dependent on sublingual buprenorphine/naloxone (prescribed or illicit)

- If have long-acting buprenorphine/naloxone on receptors
  - then injection of buprenorphine/naloxone will not cause withdrawal, but instead give agonist effects
- If no long-acting buprenorphine/naloxone on receptors
  - then injection of buprenorphine/naloxone will provide agonist effects
- Note this population may dissolve and inject buprenorphine/naloxone tablets, since they will have a ready supply if in maintenance treatment

Diversion and Parenteral Misuse

Persons abusing, but not physically dependent on opioids

- If have opioid on receptors
  - then injection of buprenorphine/naloxone may cause opioid withdrawal syndrome

- If no opioid on receptors
  - then injection of buprenorphine/naloxone will give agonist effect because the low dose of naloxone will not completely block the buprenorphine

Diversion and Sublingual Misuse

- Sublingual abuse is less likely because agonist effect onset is slower and magnitude of effect is lower
- Two groups that might abuse the combo form by sublingual route include:
  1) Persons who are physically dependent on full agonist opioids
     - Periodic abuse to control full agonist opioid withdrawal syndrome is most likely pattern
  2) Persons who are NOT physically dependent on any type of opioids
     - Experimental abuse for agonist effect is more likely in this group

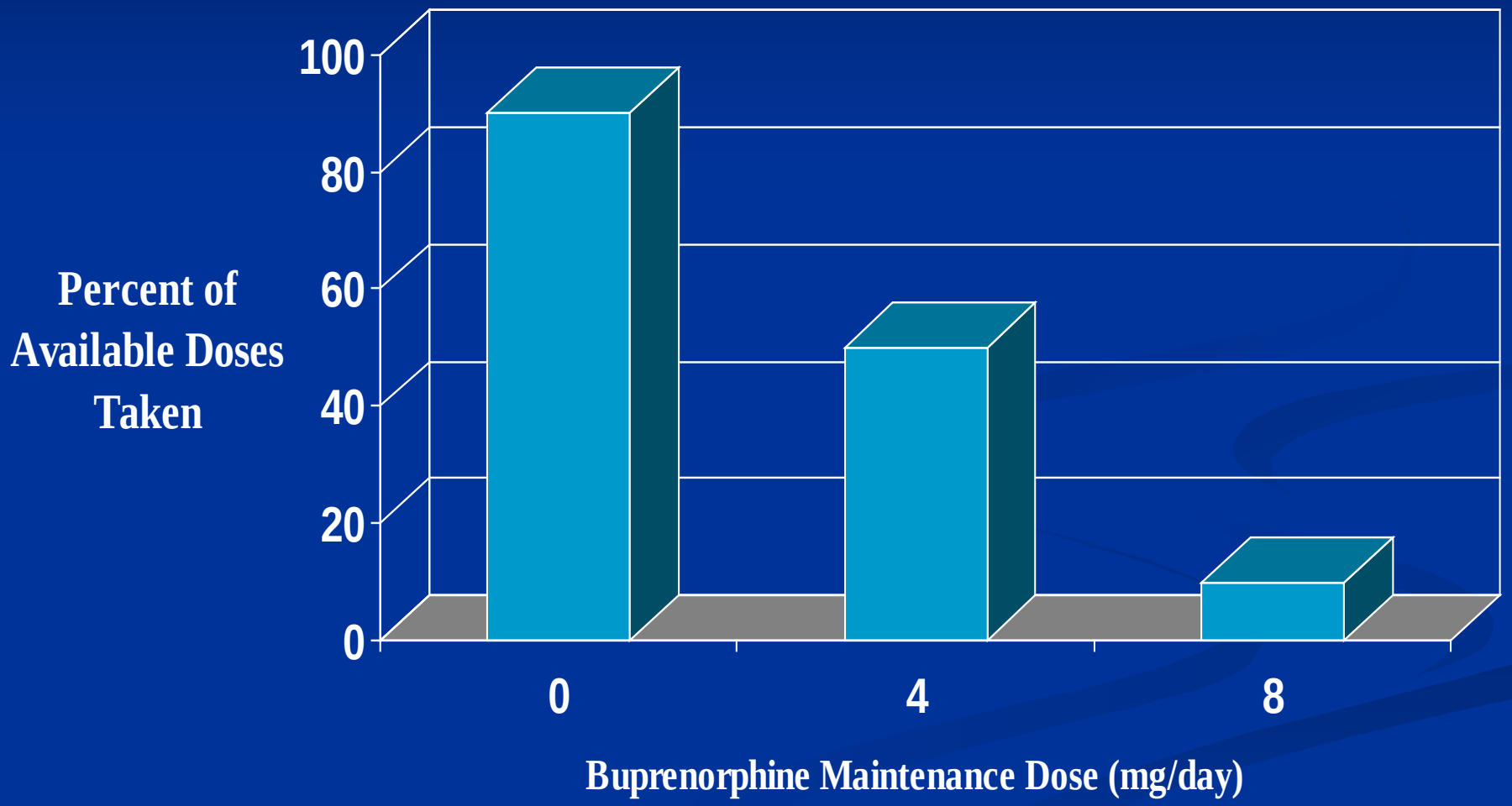
Buprenorphine Treatment

- Maintenance
- Medical Withdrawal

Buprenorphine Maintenance

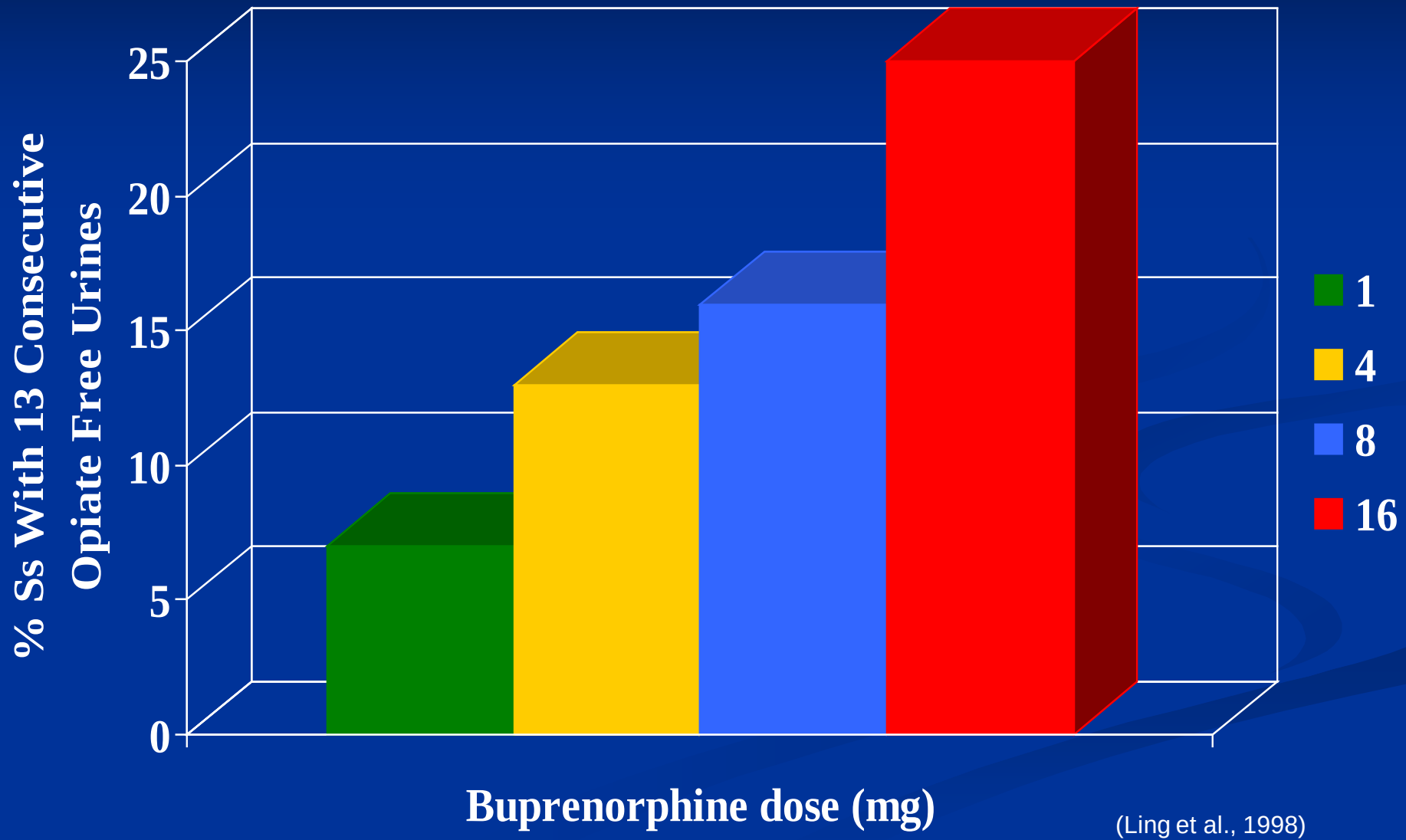
- Numerous outpatient clinical trials in people with Opioid Dependence compared efficacy with:
  - Methadone
  - LAAM
  - Placebo
- These trials reliably demonstrated that, in preventing relapse to heroin:
  - Buprenorphine is more effective than placebo
  - Buprenorphine is equally effective as moderate doses of methadone (e.g., 60 mg per day)

Heroin Self-Administration During Buprenorphine Maintenance



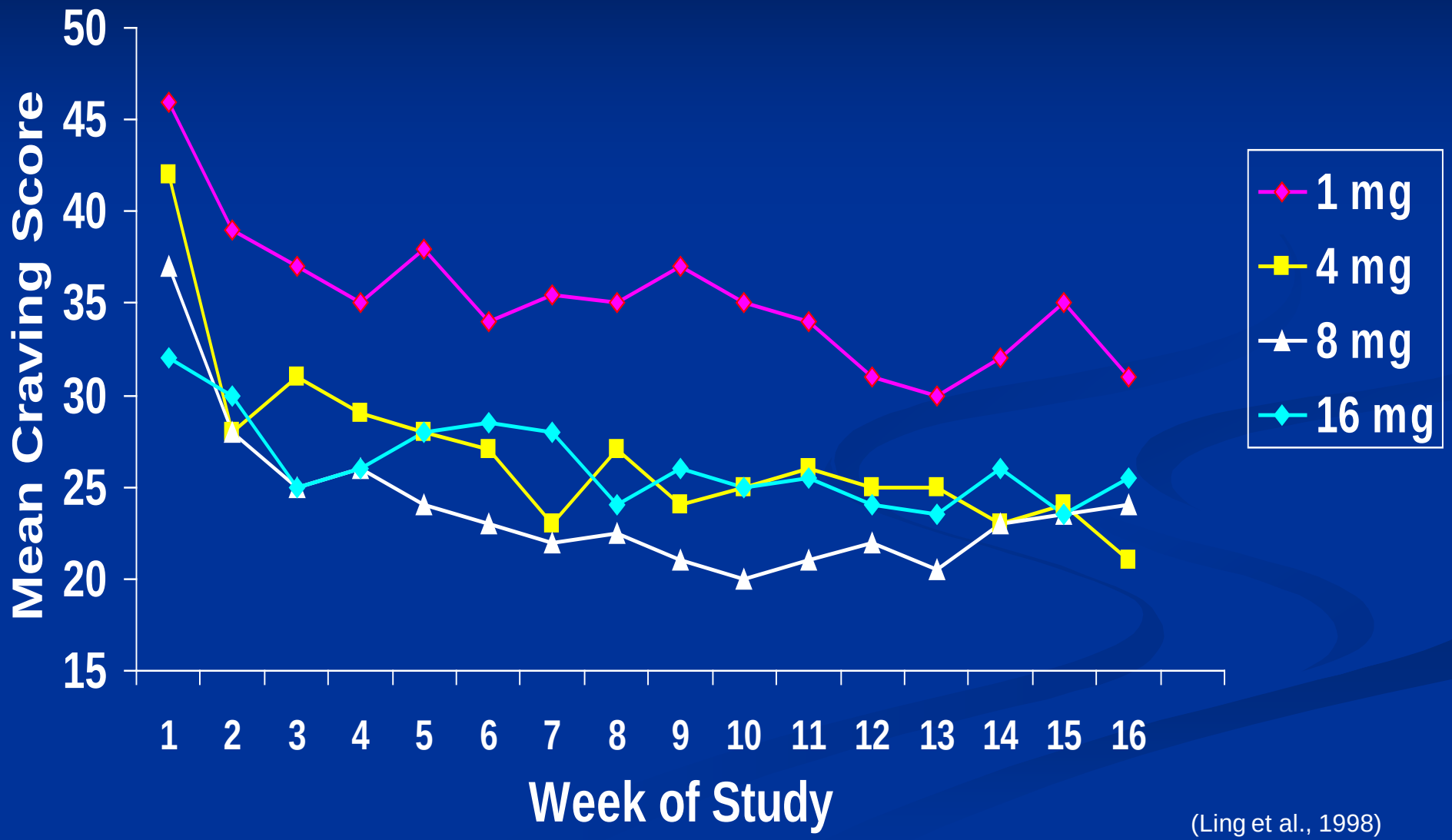
(Mello and Mendelson, 1980, Mello et al., 1982)

Different Doses of Buprenorphine: Opiate Use



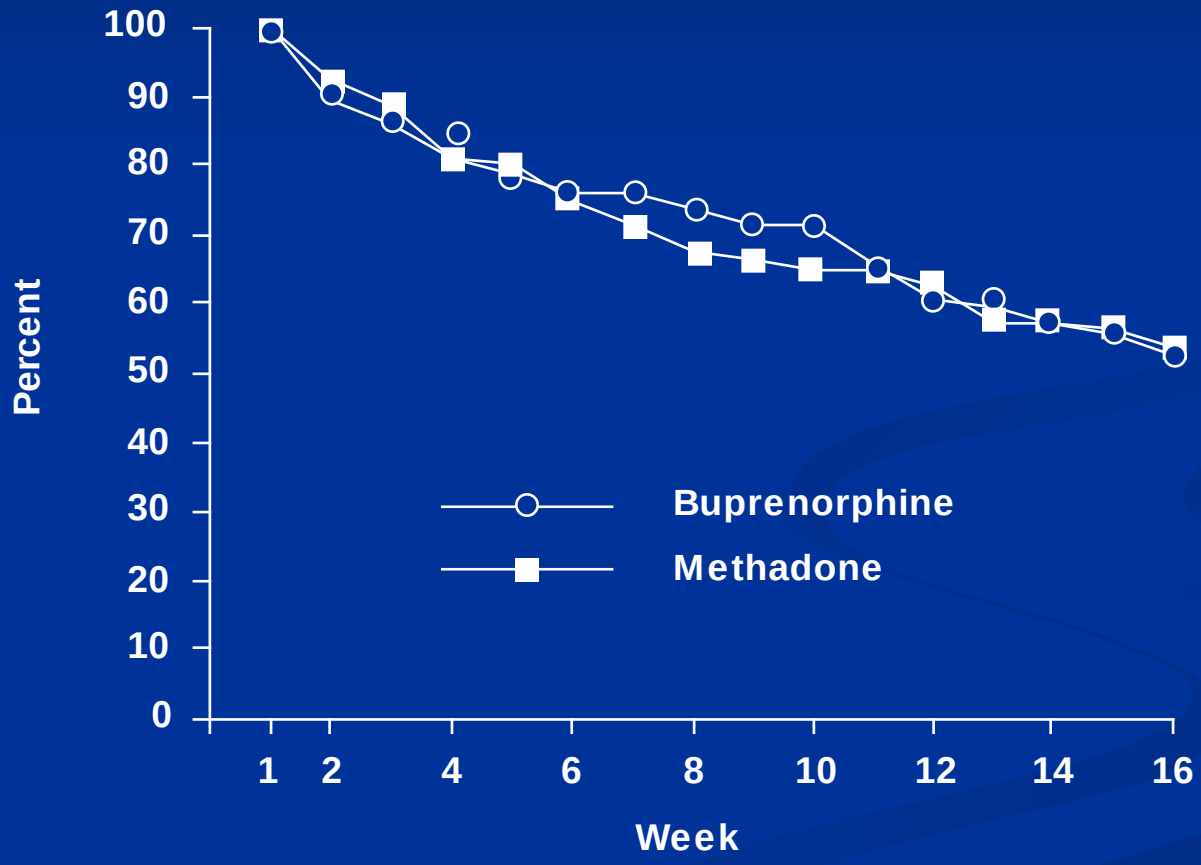
(Ling et al., 1998)

Mean Heroin Craving: 16 Week Completers



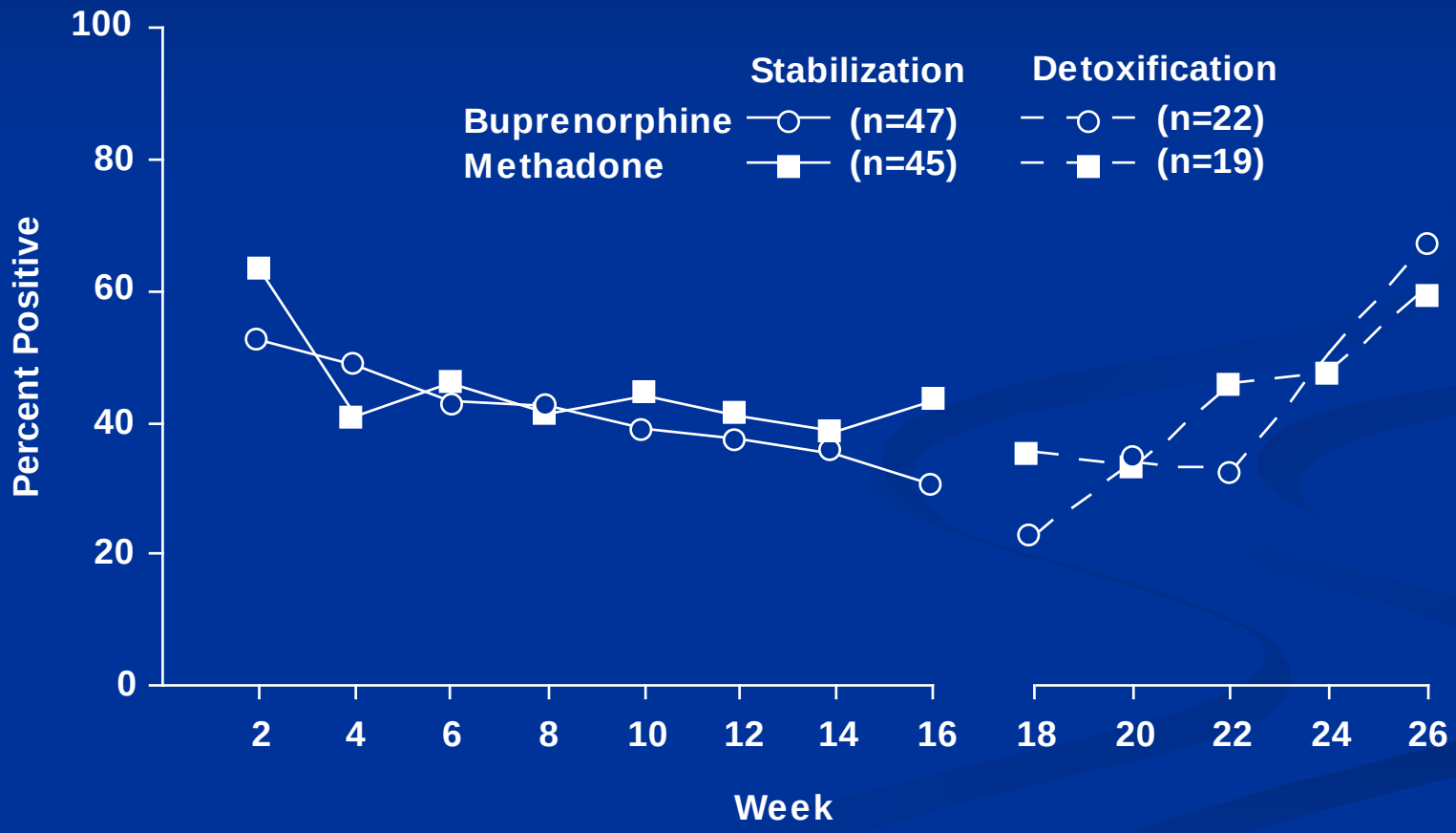
(Ling et al., 1998)

Buprenorphine – Methadone: Treatment Retention



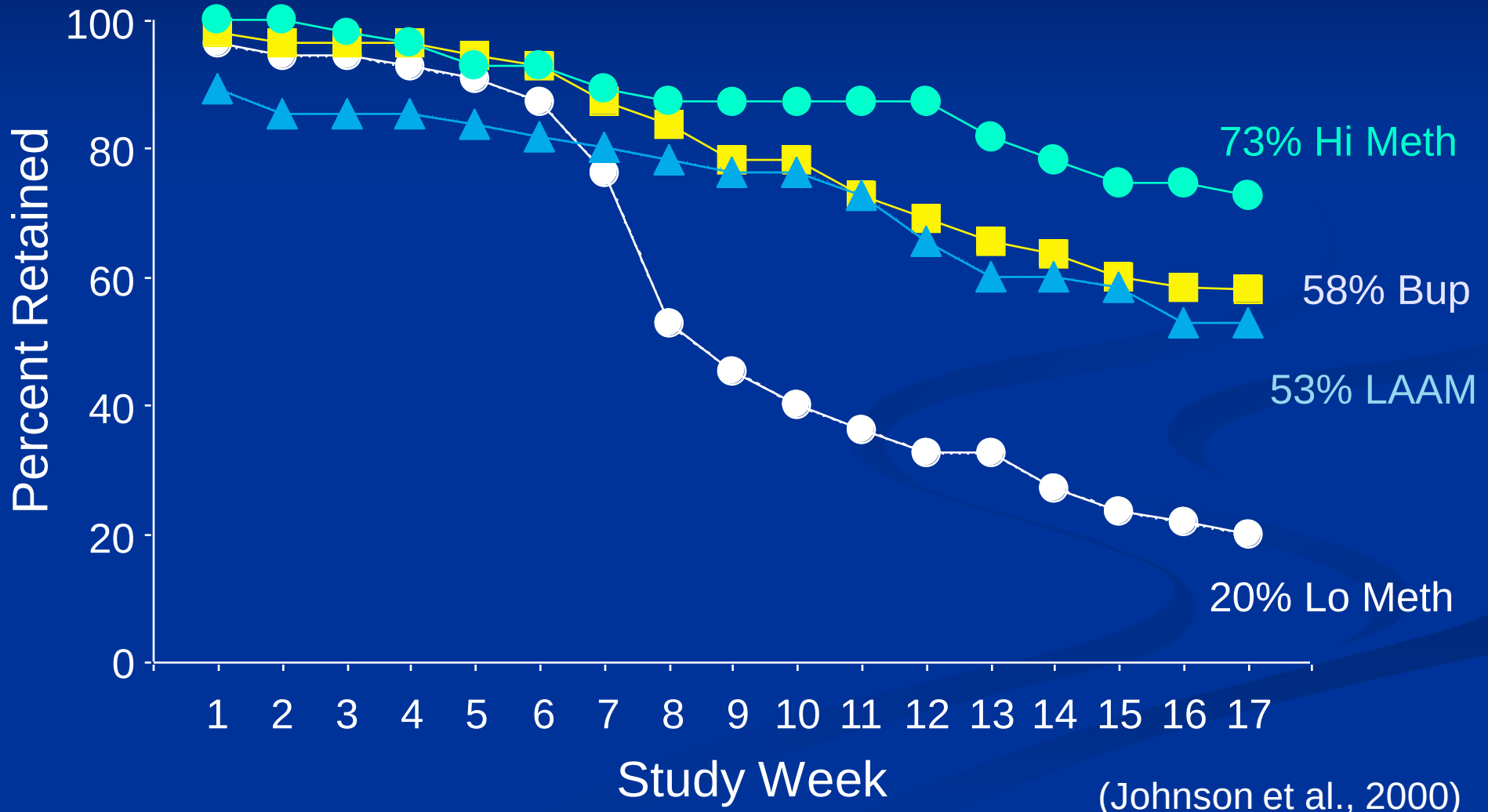
(Strain et al., 1994)

Buprenorphine – Methadone: Opioid Urine Results



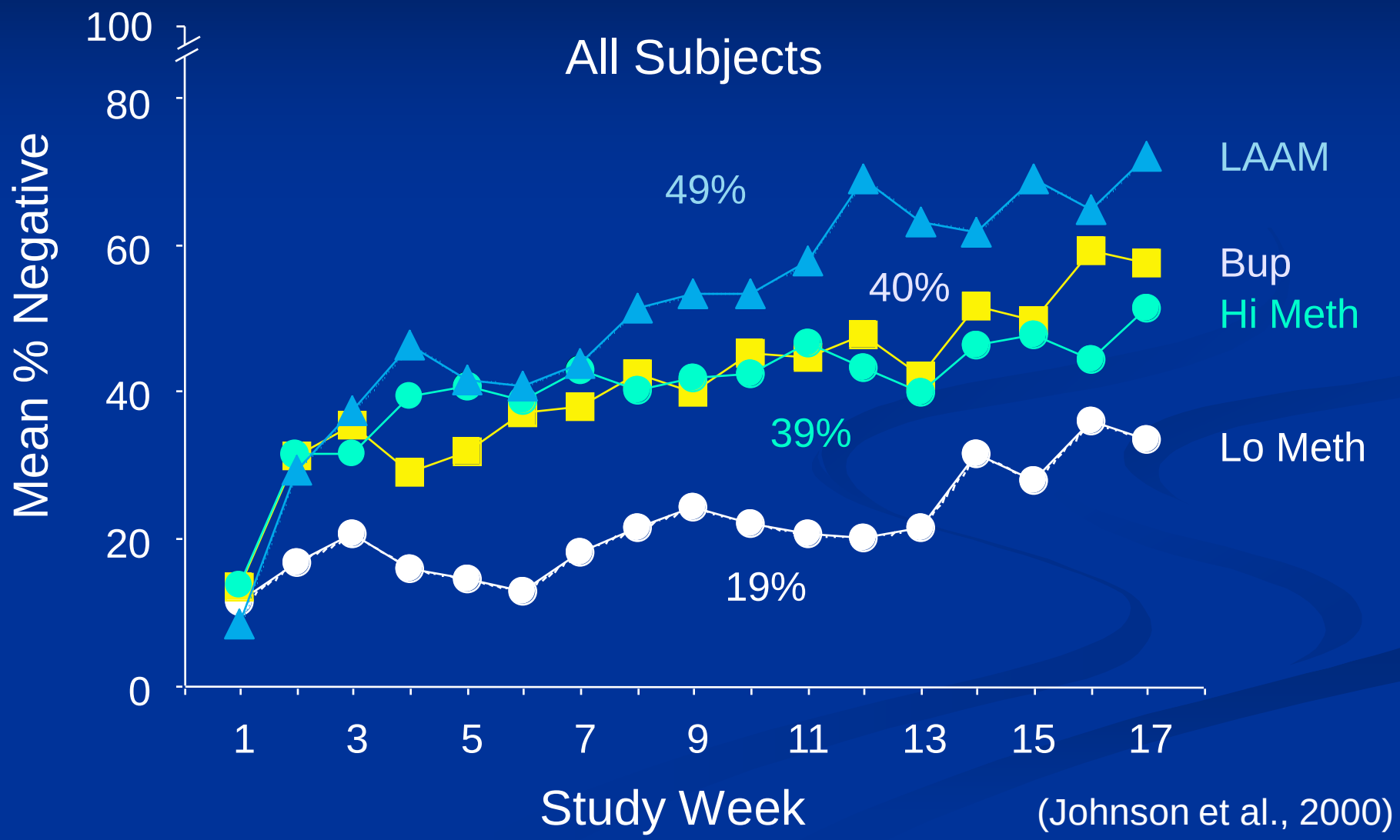
(Strain et al., 1994)

Buprenorphine, Methadone, LAAM: Treatment Retention



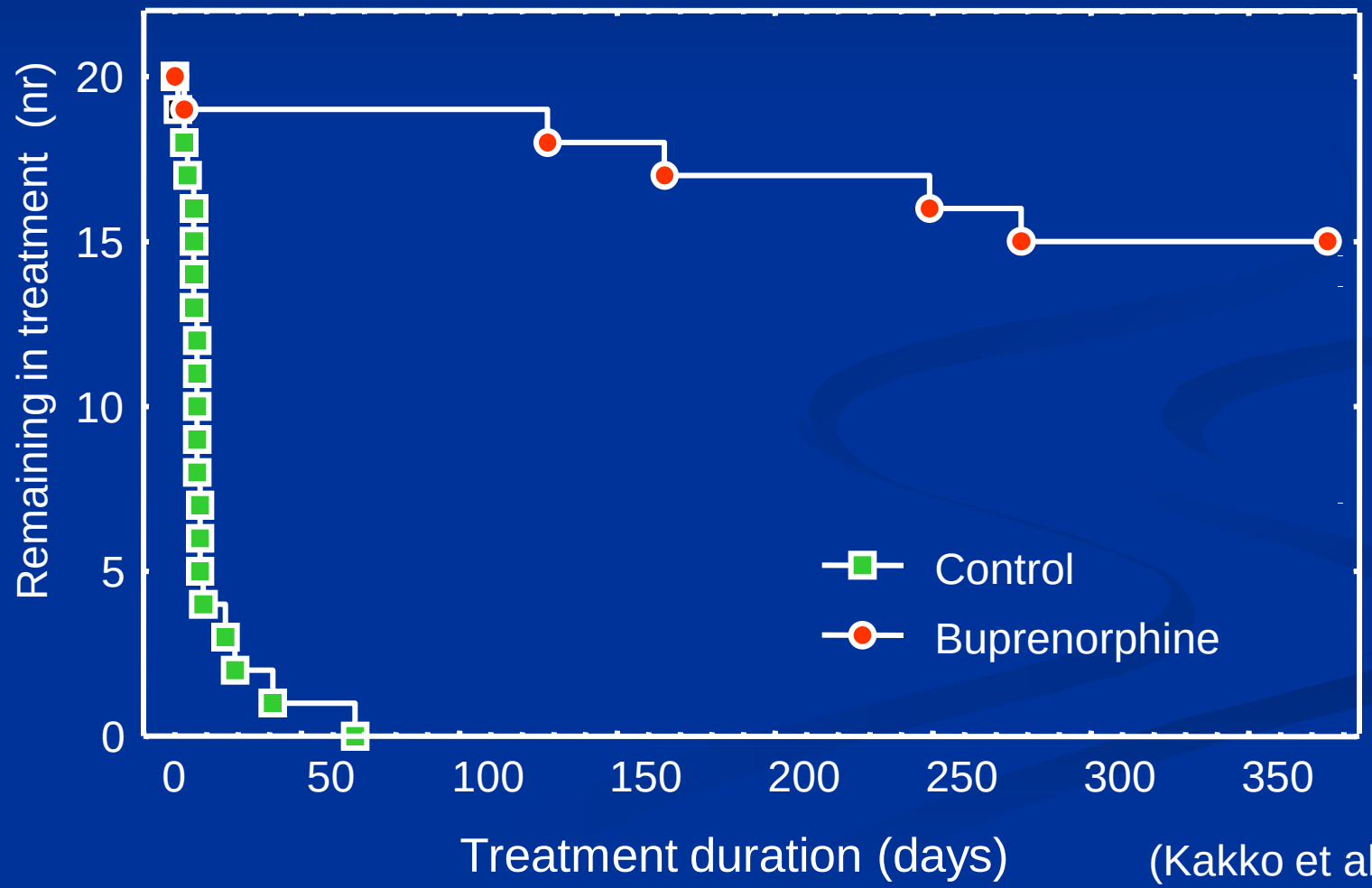
(Johnson et al., 2000)

Buprenorphine, Methadone, LAAM: Opioid Urine Results



(Johnson et al., 2000)

Buprenorphine Maintenance/Withdrawal: Retention



(Kakko et al., 2003)

Buprenorphine Dosing

- Sublingual administration
- Dissolves in 3-10 minutes
  - Tablet taste is generally well tolerated
  - Monitor dissolution
- Two tablets or strips at one time is the limit for 8/2 mg dose
- Three tablets or strips at one time is the limit for 2/0.5 mg dose

Buprenorphine: Side Effects

- Nausea/vomiting (consider precipitated withdrawal)
- Constipation
- Sedation (use of other sedating drugs or in those not currently dependent, but eligible for buprenorphine treatment by history)
- Elevations in liver transaminases (Hep C at higher risk)

Buprenorphine-Methadone Comparison

	Buprenorphine	Methadone
Regulation/ Diversion	Partial agonist May be diverted Less regulation Can be used in office-based treatment of opioid dependence	Full agonist May be diverted Toxicity risk greater Specialized centers required for treatment of opioid dependence
Dose/side Effects	Preferred is combo: bup/nlx Fewer side effects Precipitated withdrawal potential Reduced risk of overdose	Relatively high dose required for tolerance induction; continued opiate effects, sedation
Ease of Use	Induction generally requires clinical monitoring Available by prescription Withdrawal better tolerated	Induction and dosing straightforward first doses should be monitored Withdrawal challenging; Complaints of significant discomfort
Drug Interactions	No clinically significant with HIV meds except atazanavir; rifampin assoc. with withdrawal; BZD (particularly injected) and CNS depressants a concern	Numerous, especially HIV meds, TB meds, some anticonvulsants; concern about interactions with BZDs and other CNS depressants

Summary

- Buprenorphine:
  - Opioid partial agonist: less opioid effects than heroin or methadone; less potential for toxicity
  - Induction generally requires clinical monitoring
  - Withdrawal is better tolerated than for other opioids
  - Buprenorphine administration will result in precipitated withdrawal in person physically dependent on opioids if administered following recent opioid use