Efficacy and Safety of Buprenorphine

Efficacy of Buprenorphine

A. MAINTENANCE TREATMENT USING BUPRENORPHINE

B. Medically-managed withdrawal using buprenorphine

Maintenance Treatment Using Buprenorphine

- Numerous outpatient clinical trials comparing efficacy of daily buprenorphine to placebo and to methadone
- Many of these studies used the sublingual liquid form (so adjust dose accordingly when using tablets)
- Typical primary outcome measures – treatment retention, presence of opioids in urine drug test results

Maintenance Treatment Using Buprenorphine

These studies conclude:

- **Buprenorphine more effective than placebo**
- **Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)**
- **Not clear if buprenorphine can be as effective as higher doses of methadone (e.g., 80-100 mg or more per day), and therefore may not be the treatment of choice for patients with higher levels of physical dependence**

Maintenance Treatment Using Buprenorphine

Following slides briefly review representative studies:

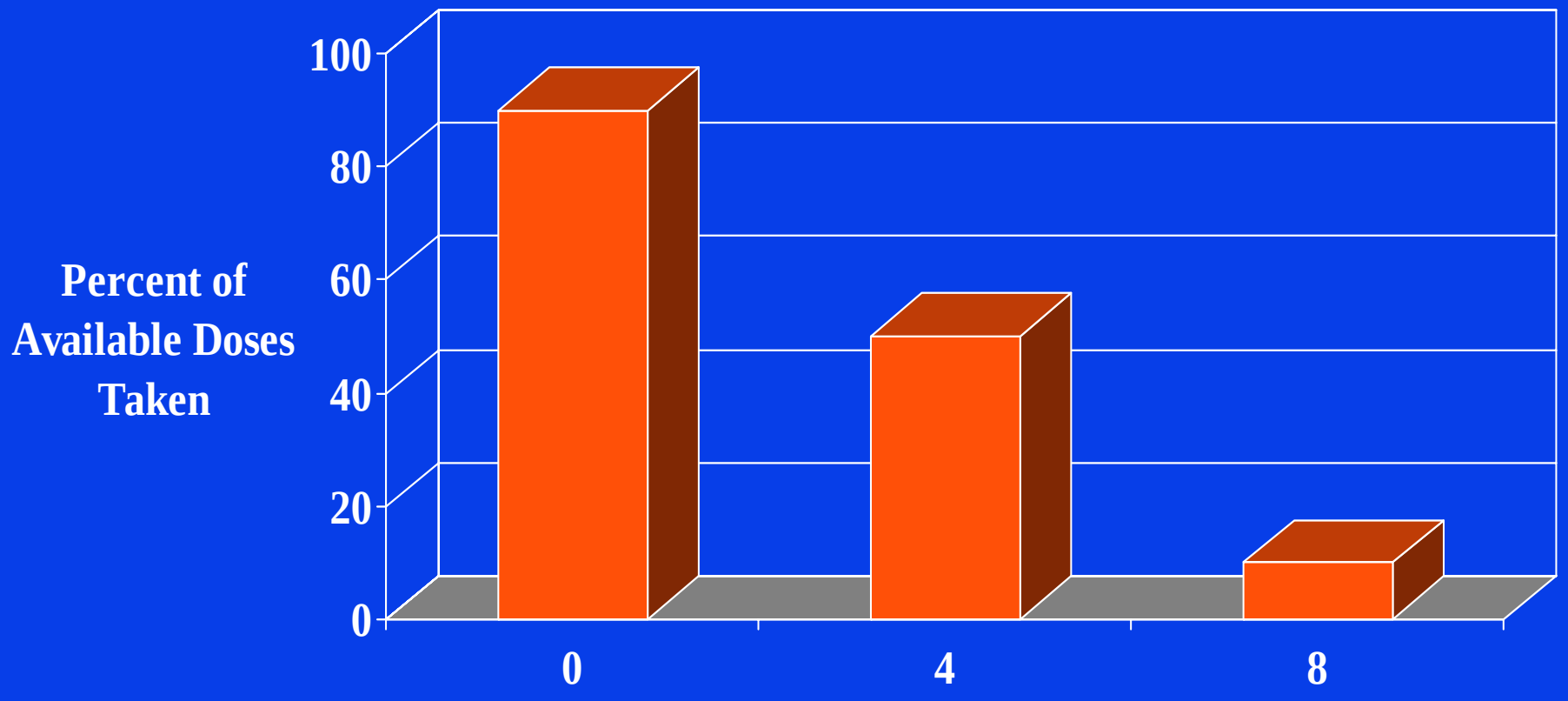
- **BUPRENORPHINE'S EFFECT ON HEROIN SELF-ADMINISTRATION**
- **Comparison of different doses of sublingual buprenorphine**
- **Buprenorphine-methadone flexible dose comparison**
- **Buprenorphine, methadone, LAAM comparison**

Maintenance Treatment Using Buprenorphine

Buprenorphine's effects on heroin self-administration:

- Inpatient study with opioid dependent volunteers (men; n=10), maintained on placebo or buprenorphine (SQ)
- Dose of buprenorphine was up to 8 mg/day
- Allowed to self-administer IV heroin using an operant task

Heroin Self-Administration During Buprenorphine Maintenance



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

Maintenance Treatment Using Buprenorphine

Buprenorphine's effects on heroin self-administration (Mello and Mendelson, 1980) *continued*:

- Early study showing that buprenorphine could suppress heroin self-administration
- Also shows a dose effect for buprenorphine (although only one subject on the 4 mg dose)
- Suppressed significant (but not all) heroin self-administration

Maintenance Treatment Using Buprenorphine

Following slides briefly review representative studies:

- **Buprenorphine's effects on heroin self-administration**
- **COMPARISON OF DIFFERENT DOSES OF SUBLINGUAL BUPRENORPHINE**
- **Buprenorphine-methadone flexible dose comparison**
- **Buprenorphine, methadone, LAAM comparison**

Maintenance Treatment Using Buprenorphine

Comparison of different doses of sublingual buprenorphine:

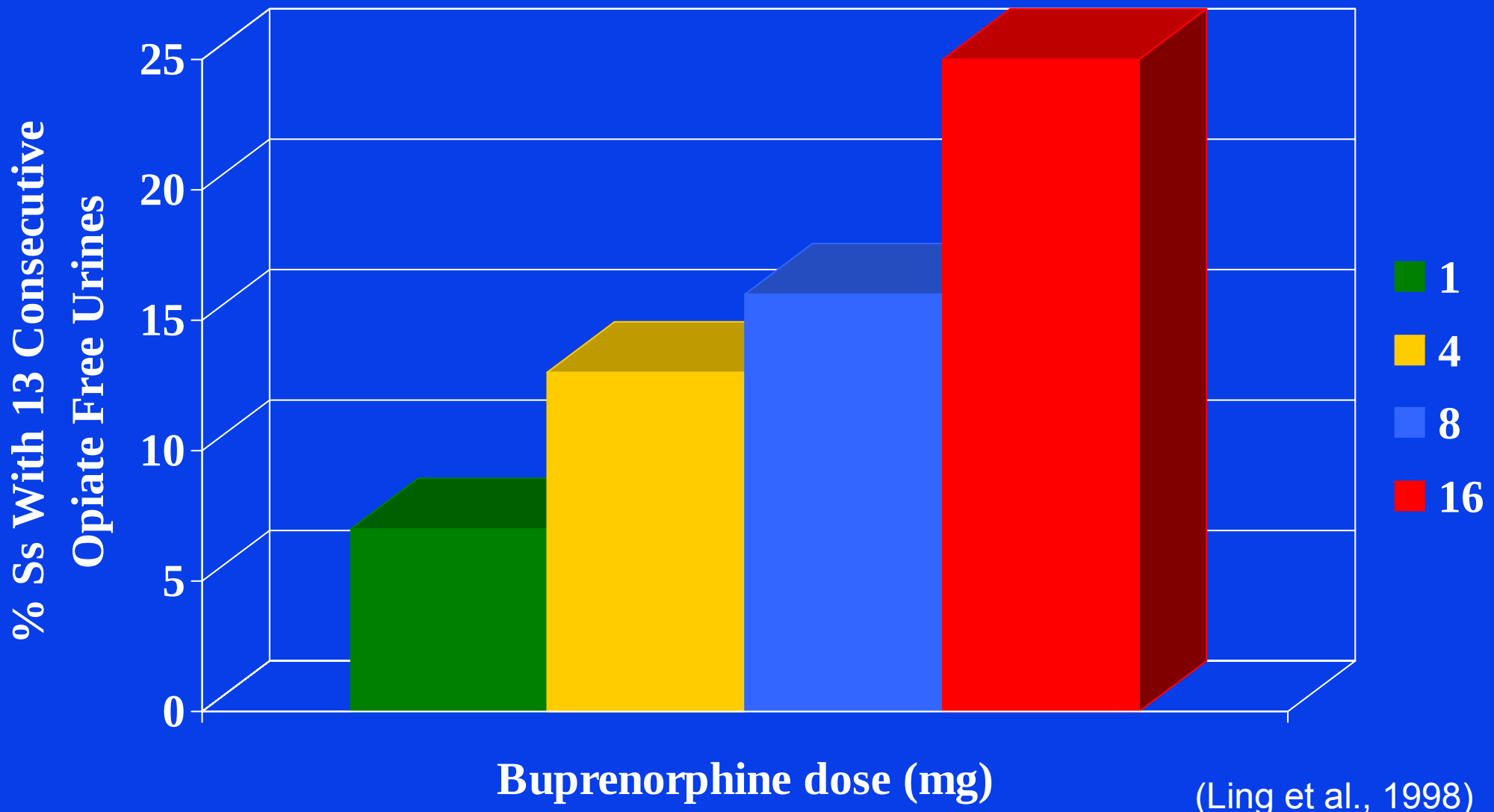
- Multi-site (n=12), 16 week outpatient study in USA
- Primarily a comparison of 8 vs. 1 mg/day SL buprenorphine solution; also included 4 and 16 mg conditions (n=736)
- 1 mg condition meant to be a placebo-like comparison
- Randomized, double-blind

Maintenance Treatment Using Buprenorphine

Comparison of different doses of sublingual buprenorphine:

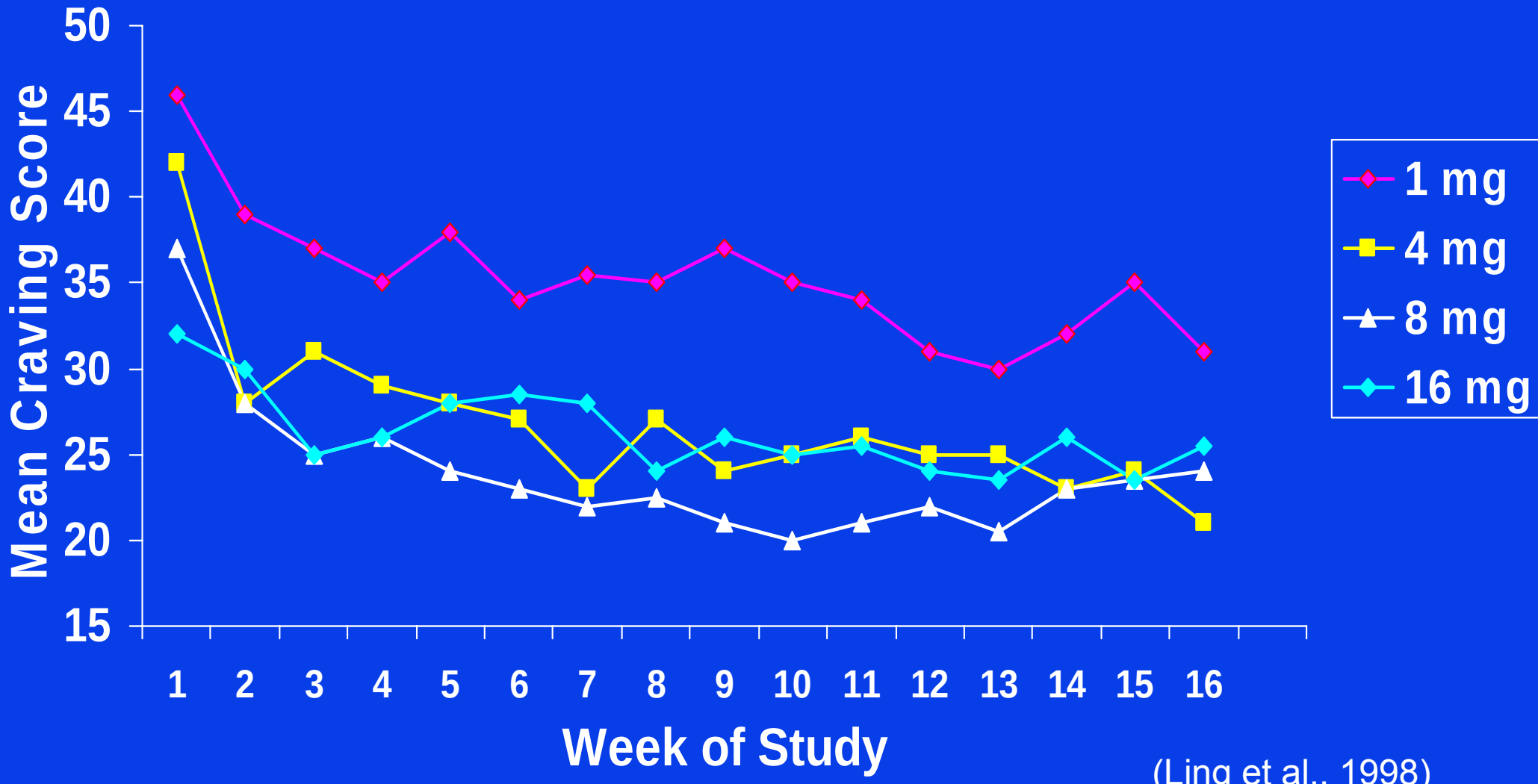
- Primary outcome measures for the study:
  - Treatment retention
  - Illicit opioid use as determined by urine testing (urine samples collected and tested 3 times per week)
  - Self-reports of opioid craving
  - Global ratings of functioning made by patient and staff
- Safety outcome measures also collected and reported

Different Doses of Buprenorphine: Opiate Use



(Ling et al., 1998)

Mean Heroin Craving: 16 Week Completers



(Ling et al., 1998)

Maintenance Treatment Using Buprenorphine

Comparison of different doses of sublingual buprenorphine:

- Large clinical trial that can be interpreted as a placebo-controlled study of buprenorphine (important for FDA approval process)
- Showed efficacy and safety of 8 mg/day SL buprenorphine solution; also showed dose-related efficacy

Maintenance Treatment Using Buprenorphine

Following slides briefly review representative studies:

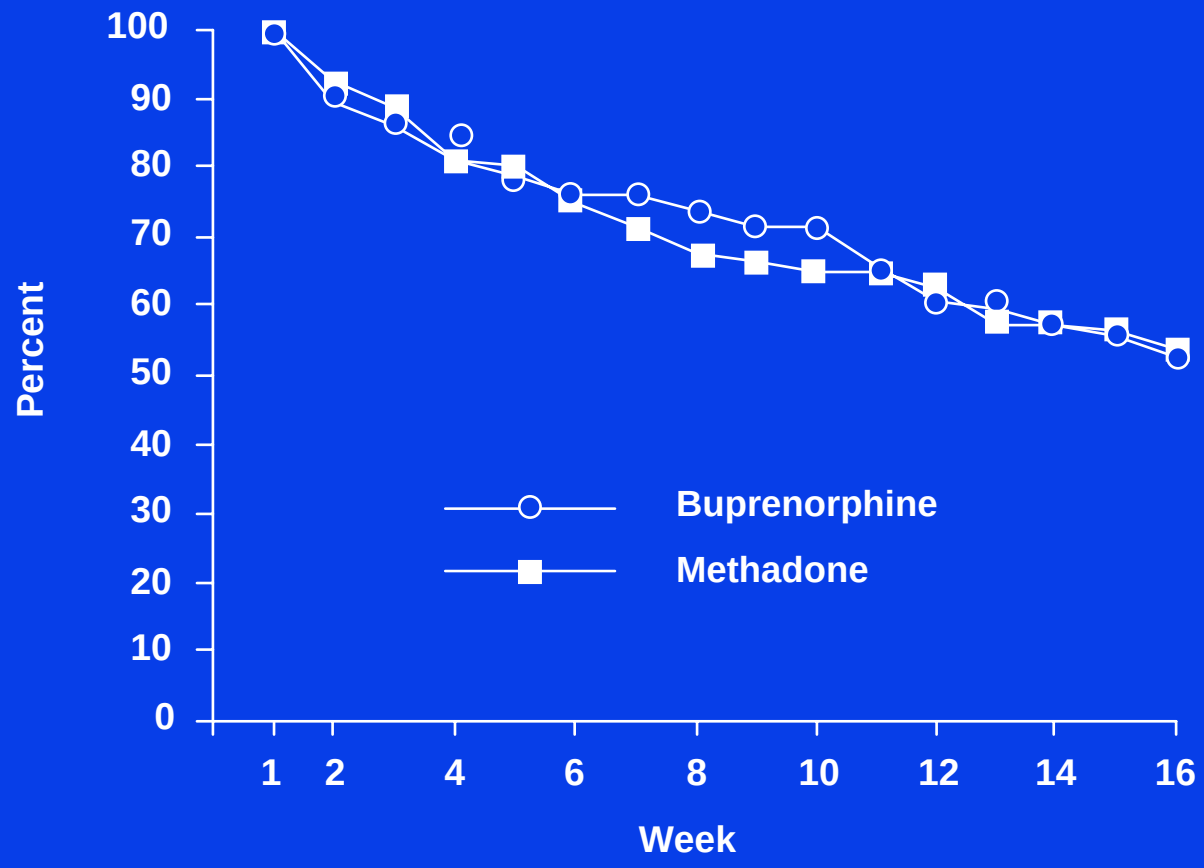
- **Buprenorphine's effects on heroin self-administration**
- **Comparison of different doses of sublingual buprenorphine**
- **BUPRENORPHINE-METHADONE FLEXIBLE DOSE COMPARISON**
- **Buprenorphine, methadone, LAAM comparison**

Maintenance Treatment Using Buprenorphine

Buprenorphine-methadone flexible dose comparison:

- 16 week outpatient randomized, double-blind clinical trial, single site (n=164)
- Utilized double-blind flexible dosing procedure (50-90 mg/day of methadone, 8-16 mg/day SL buprenorphine solution)

Buprenorphine – methadone: treatment retention



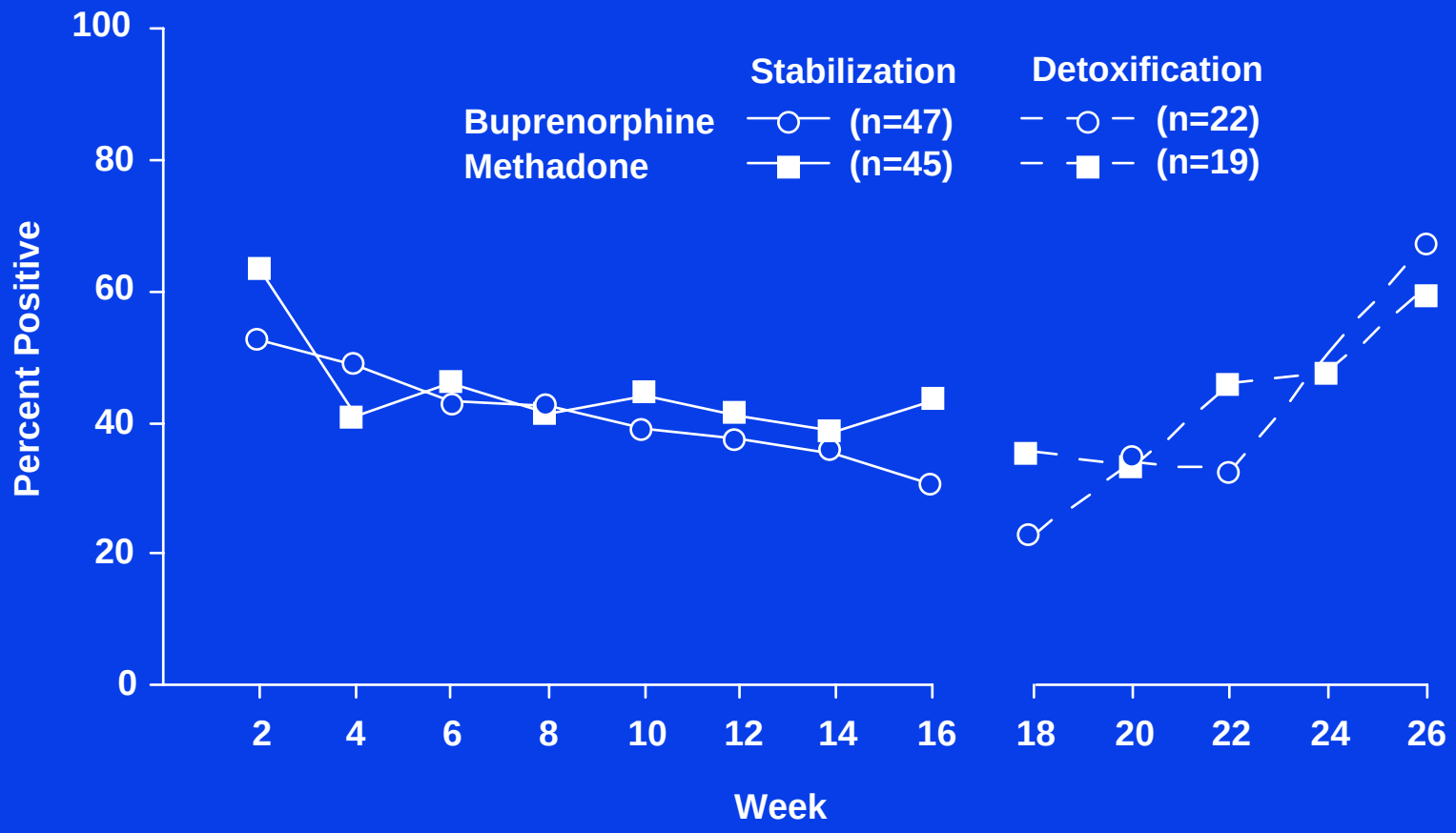
(Strain et al., 1994)

Maintenance Treatment Using Buprenorphine

Buprenorphine-methadone flexible dose comparison:

After the 16 weeks of maintenance dosing, participants underwent a ten week withdrawal from methadone or buprenorphine. As can be seen in the next slide, participants tended to relapse in their opioid use as both medications were withdrawn, with no significant difference between groups during that ten week period.

Buprenorphine – methadone: opioid urine results



(Strain et al., 1994)

Maintenance Treatment Using Buprenorphine

Buprenorphine-methadone flexible dose comparison:

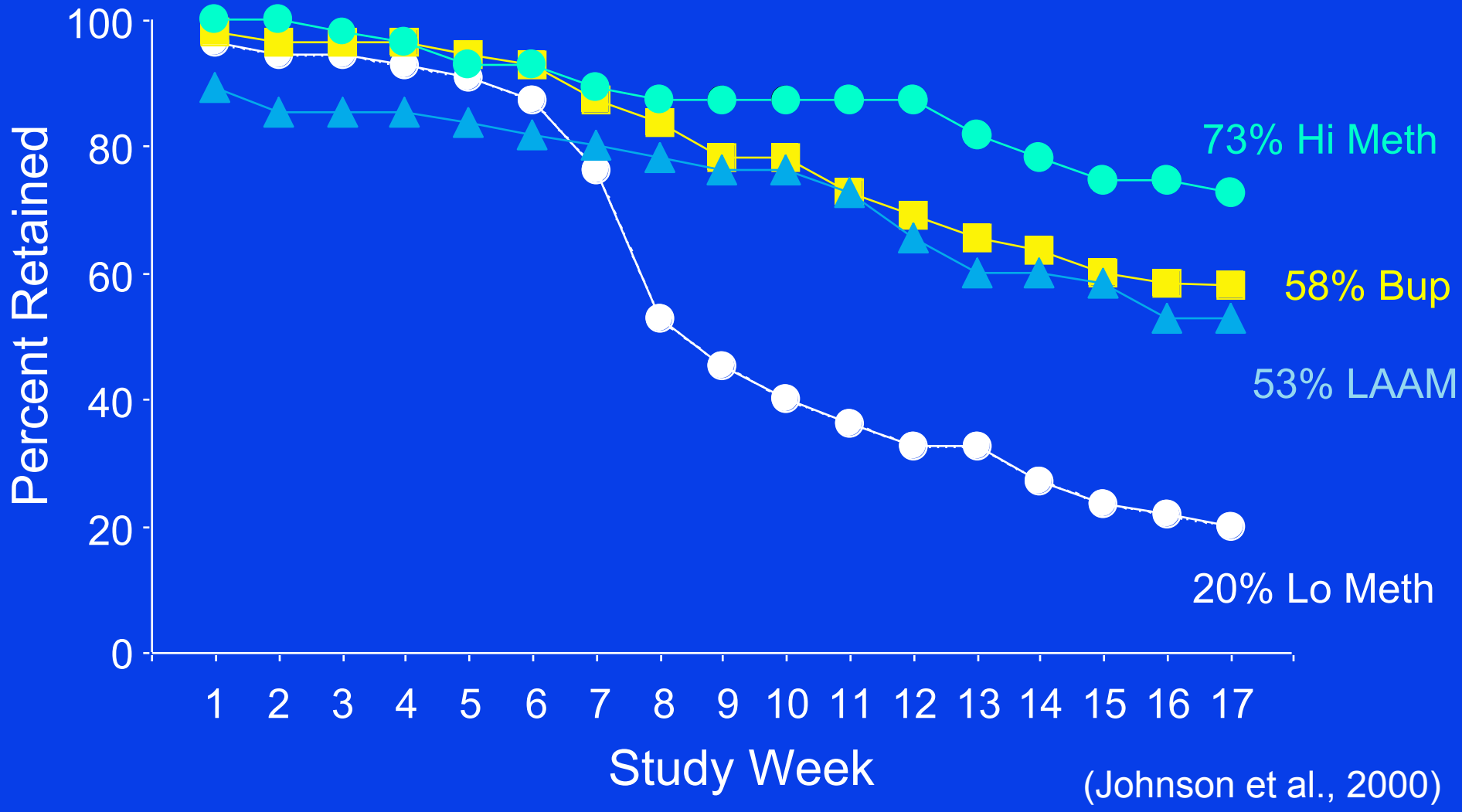
- Flexible dosing in the study ensured comparison of medication efficacy rather than dose efficacy, and showed that there are very similar outcomes when comparable doses are used

Maintenance Treatment Using Buprenorphine

Buprenorphine, methadone, LAAM comparison:

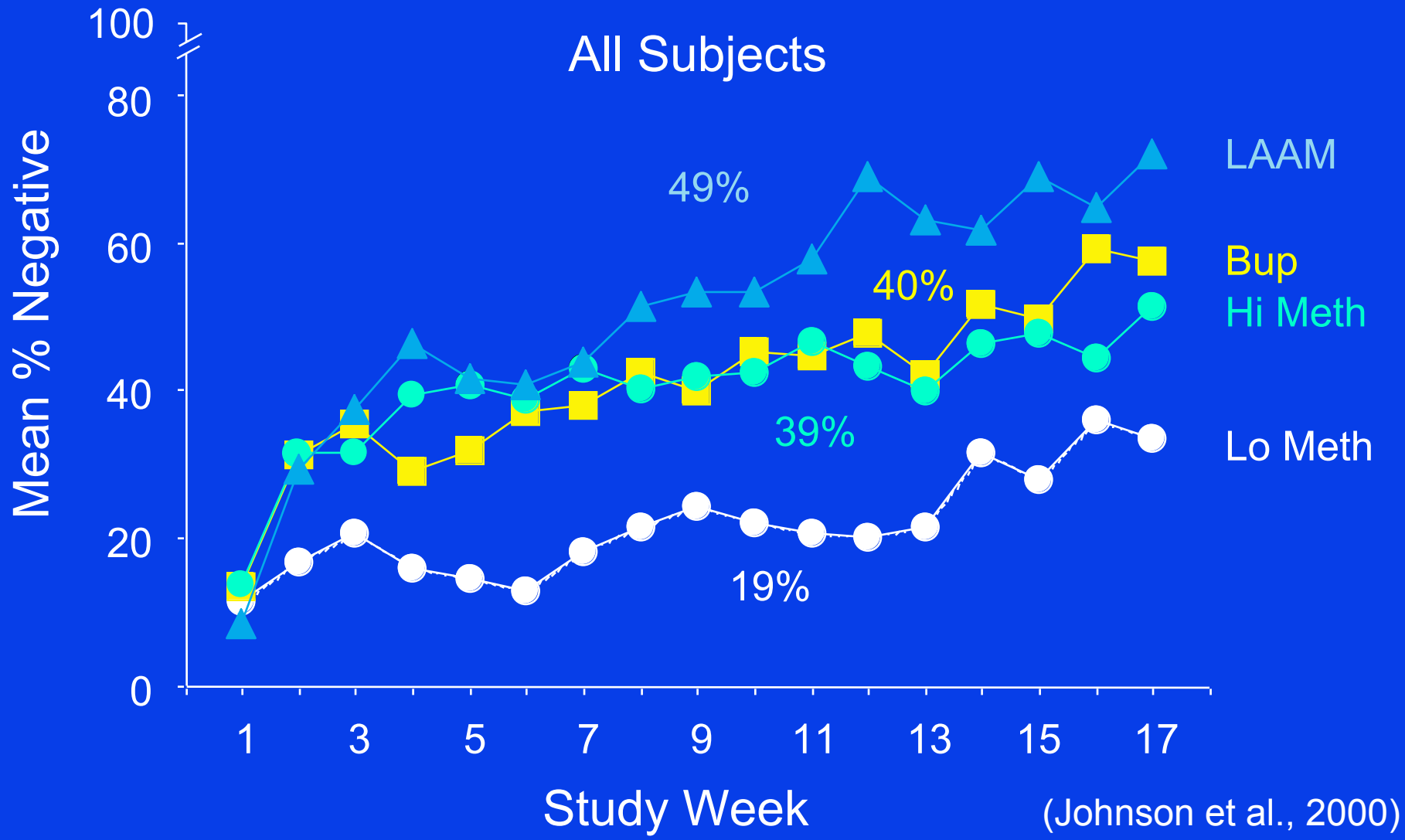
- 17 week outpatient randomized, double-blind clinical trial, single site (n=220)
- Four conditions with flexible dosing for three of the four: high dose methadone, LAAM (3x per week), buprenorphine (3x per week), and low dose methadone

Buprenorphine, Methadone, LAAM: Treatment Retention



(Johnson et al., 2000)

Buprenorphine, Methadone, LAAM: Opioid Urine Results



(Johnson et al., 2000)

Efficacy of Buprenorphine

A. Maintenance treatment using buprenorphine

B. MEDICALLY-MANAGED WITHDRAWAL USING BUPRENORPHINE

Withdrawal Using Buprenorphine

- **Withdrawal is not as well studied as maintenance**
- **Most studies have looked primarily at buprenorphine maintenance, not withdrawal**

Withdrawal Using Buprenorphine

- In general, withdrawal using opioids (e.g., methadone) has had poor outcomes after withdrawal was completed
- Results after withdrawal using buprenorphine may be better (may have a milder withdrawal syndrome)
- However, overall, withdrawal outcomes are poorer than maintenance results

Withdrawal Using Buprenorphine

Following slides briefly review representative studies:

- Comparison of buprenorphine maintenance to withdrawal
- Comparison of buprenorphine versus clonidine withdrawal

Buprenorphine Maintenance/Withdrawal

Buprenorphine maintenance vs. withdrawal:

Double-blind, random assignment to:

- 16 mg/day SL buprenorphine tablets, or
- 6 day buprenorphine withdrawal followed by placebo

20 patients per group

Used tablets of buprenorphine, placebo

Kakko et al. 2003

Buprenorphine Maintenance/Withdrawal

Comparison of buprenorphine maintenance vs. withdrawal:

- First week of study was inpatient; study lasted one year; take home doses allowed after 6 months of treatment
- Outcome measures included
  - treatment retention
  - urine samples that were collected under supervision and tested three times per week
  - ASI scores

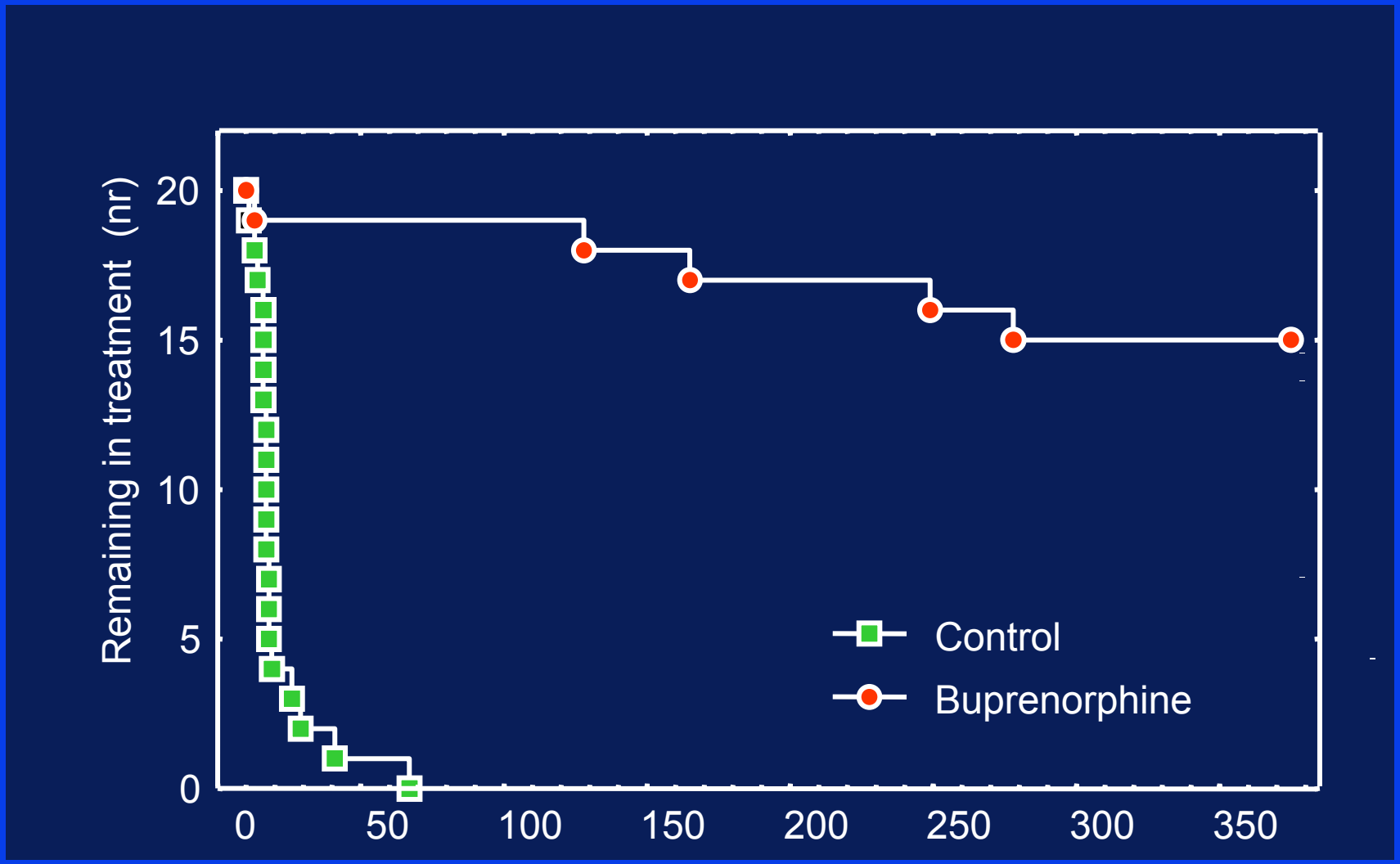
Buprenorphine Maintenance/Withdrawal

Comparison of buprenorphine maintenance vs. withdrawal:

All participants also received a relatively rich set of psychosocial treatments

- group and individual counseling
- assistance with various social service agencies (for example, for housing and employment)

Buprenorphine Maintenance/Withdrawal: Retention



(Kakko et al., 2003)

Buprenorphine Maintenance/Withdrawal: Mortality

	Placebo	Buprenorphine	Cox regression
Dead	4/20 (20%)	0/20 (0%)	χ^2=5.9; p=0.015

(Kakko et al., 2003)

Buprenorphine Maintenance/Withdrawal

Comparison of buprenorphine maintenance vs. withdrawal:

- Shows both the efficacy of maintenance treatment, and the poor outcomes associated with withdrawal (even when provided within the context of a relatively rich set of psychosocial treatments)

Safety of Buprenorphine

A. Overview and Side Effects

B. Liver Function Tests

C. Teratogenesis

D. Precipitated withdrawal

E. Overdose

F. Drug interactions

Overview to Safety and Side Effects

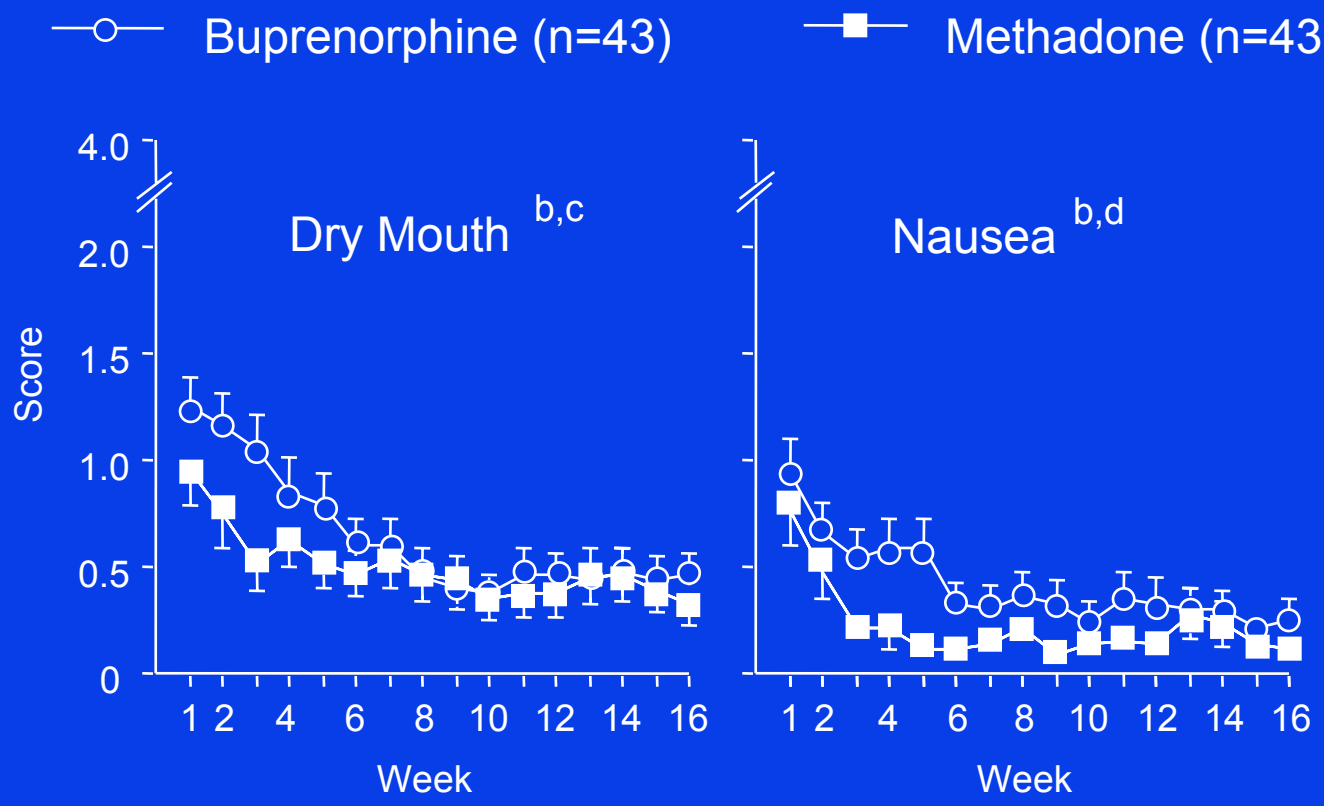
Highly safe medication (under both acute and chronic dosing circumstances)

Also safe if inadvertently taken by someone not dependent on opioids (because of poor oral bioavailability and the ceiling on maximal effects)

Overview to Safety and Side Effects

- **Primary side effects: like other mu agonist opioids such as methadone (e.g., nausea, constipation)**
- **Anecdotal reports indicate that symptoms may be less severe**

Buprenorphine and Methadone: Side Effects



[a] significant **group** effect ($p<0.01$)

[b] significant **time** effect ($p<0.01$)

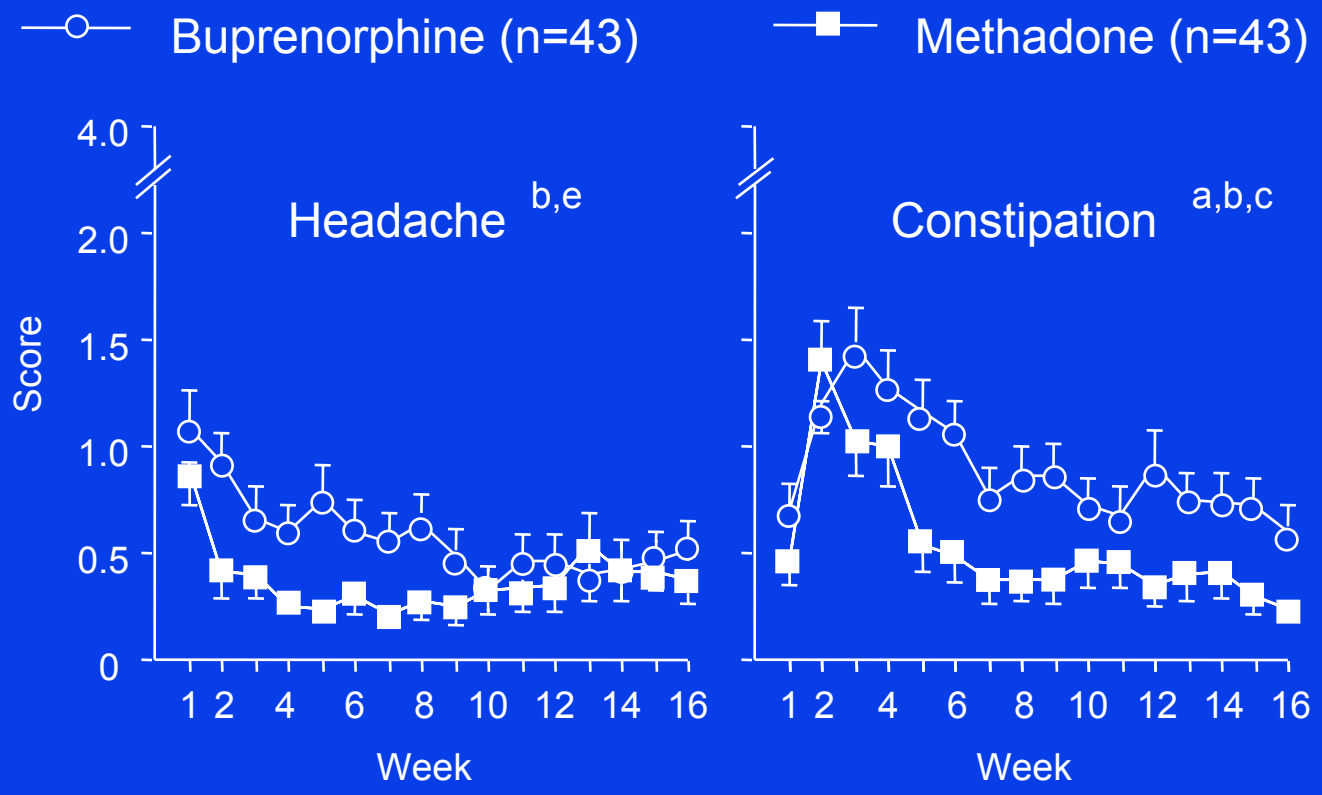
[c] trend for significant group x time effect ($0.05 \leq p<0.10$)

[d] trend for significant group effect ($0.05 \leq p<0.10$)

[e] **significant** group x time effect ($p<0.05$)

(Strain et al 1994)

Buprenorphine and Methadone: Side Effects



[a] significant group effect ($p<0.01$)

[b] significant time effect ($p<0.01$)

[c] trend for significant group x time effect ($0.05 \leq p < 0.10$)

[d] trend for significant group effect ($0.05 \leq p < 0.10$)

[e] significant group x time effect ($p<0.05$)

(Strain et al 1994)

Overview to Safety and Side Effects

- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance

Safety of Buprenorphine

A. Overview and Side Effects

B. LIVER FUNCTION TESTS

C. Teratogenesis

D. Precipitated withdrawal

E. Overdose

F. Drug interactions

Liver Function Tests

Two types of reports of buprenorphine's effects on liver function tests:

- **Case reports – IV administration of high acute doses of buprenorphine in patients with hepatitis**
- **Retrospective chart review of SL buprenorphine use in patients with a history of hepatitis**

Liver Function Tests

Case reports:

Four case reports of hepatitis:

Transaminase increases, 13-50x normal, with IV buprenorphine in patients infected with Hepatitis C

Liver Function Tests

Case reports *(continued)*:

Mechanism:

Buprenorphine inhibits hepatic mitochondrial function at high concentrations

This magnitude of effect should not occur with sublingual administration

Liver Function Tests

Retrospective chart review:

Study of 120 patients treated with various doses of sublingual buprenorphine for more than 40 days

Retrospective chart review *(continued):*

72 patients with hepatitis:

Median increase in ALT: 8.5 (-12 to 54)

AST: 9.5 (-8 to 32)

48 patients without hepatitis:

Median increase in ALT: 0 (-7 to 8)

AST: 1 (-6 to 4.5)

Liver Function Tests

Buprenorphine and Liver Function Tests: Conclusions

- Patients with a history of hepatitis are at increased risk for elevations of liver function tests when treated with buprenorphine, but these increases appear to be mild and may be clinically insignificant
- Acute intravenous use of buprenorphine can result in high elevations of liver function tests in patients with a history of hepatitis

Safety of Buprenorphine

A. Overview and Side Effects

B. Liver Function Tests

C. TERATOGENESIS

D. Precipitated withdrawal

E. Overdose

F. Drug interactions

Teratogenesis

- Limited information about use of buprenorphine in pregnant, opioid dependent women
- No reports of teratogenic effects (but limited number of cases)
- Incidence of Neonatal Abstinence Syndrome was significantly lower with buprenorphine vs. methadone
- Review of buprenorphine use in pregnancy is in the lecture on Special Populations

Precipitated Withdrawal

- Buprenorphine-precipitated withdrawal seen in controlled studies has been mild in intensity and of short duration
- The likelihood for buprenorphine-precipitated withdrawal is low, and even when it does occur, it is mild in intensity and short in duration

Precipitated Withdrawal

Risk factors that increase the possibility of buprenorphine-related precipitated withdrawal are:

- higher levels of physical dependence,
- a short time interval between last use of an opioid and first dose of buprenorphine
- higher first doses of buprenorphine

Overdose with Buprenorphine

- Low risk of clinically significant problems
- No reports of respiratory depression in clinical trials comparing buprenorphine to methadone
- Buprenorphine's ceiling effect means it is less likely to produce clinically significant respiratory depression. However, overdose where buprenorphine is combined with other CNS depressants may be fatal (reviewed later in this section)

Overdose with Buprenorphine

- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression or other significant adverse events
- Overdose of buprenorphine combined with other drugs may be associated with severe adverse events (reviewed below)

Drug Interactions with Buprenorphine

1. Benzodiazepines and other sedating drugs
2. Medications metabolized by cytochrome P450 3A4
3. Opioid antagonists
4. Opioid agonists

Benzodiazepines and Other Sedating Drugs

- Reports of deaths when buprenorphine injected along with injected benzodiazepines
  - Reported from France, where tablets available (appears patients dissolve and inject tablets)

Benzodiazepines and Other Sedating Drugs

- Probably possible for this to occur with other sedatives
- Mechanism leading to death in these cases is not known
- Not clear if any patients have died from use of sublingual buprenorphine combined with oral benzodiazepine. Most deaths appear to have been related to injection of the combination of dissolved buprenorphine tablets with benzodiazepine.

Benzodiazepines and Other Sedating Drugs

Note that the combination product (buprenorphine with naloxone, Suboxone®) is designed to decrease the likelihood that people will dissolve and inject buprenorphine

Cytochrome P450 3A4

- Several medications or substances interact with the P450 3A4 enzyme system – either as inhibitors, inducers, or substrates.
- An extensive list can be found in the Buprenorphine Guidelines document (and at www.drug-interactions.com)

Cytochrome P450 3A4

Cytochrome P450 3A4 inhibitors

- Azole antifungals
- Macrolide antibiotics
- Protease inhibitors (Ritonavir greater than Indinavir, which is greater than Saquinavir – potential to inhibit buprenorphine N-dealkylation) in vitro

Cytochrome P450 3A4

Cytochrome P450 3A4 inducers

- Phenobarbital, carbemazepine, phenytoin, rifampicin, efavirenz, lopinavir
- Efavirenz has been shown to decrease concentrations of buprenorphine and nor-buprenorphine, but without associated opioid withdrawal symptoms (as seen with methadone and efavirenz treatment); no effect of buprenorphine on efavirenz concentrations at standard clinical doses
- Important to treatment of HIV disease in opioid dependent patients

(Note limited controlled studies that have directly examined these possible interactions)

Opioid Antagonists

- Combination tablet containing buprenorphine/naloxone is safe and when used as indicated
- But, avoid prescribing buprenorphine with an opioid antagonist such as naltrexone – for example, in a patient with combined opioid and alcohol dependence
- While buprenorphine has low level of physical dependence, it may be possible to precipitate withdrawal with an opioid antagonist in buprenorphine-maintained patients

Opioid Agonists

- The combination of an opioid agonist with buprenorphine should be viewed as a possible contraindication
- Use caution if combining an opioid agonist (for example, morphine for pain relief) with buprenorphine – possible that buprenorphine could precipitate withdrawal under certain circumstances

Summary

- Buprenorphine/naloxone is effective for the treatment of opioid dependence; maintenance more effective than medical withdrawal (detoxification)
- Buprenorphine/naloxone has a good safety profile
- Buprenorphine must be used with caution in those receiving other medications:
  - Opioids
  - Opioid Antagonists
  - Benzodiazepines
  - Drugs that induce or inhibit Cytochrome P 450 3A4