

# The Science Behind Buprenorphine

## Dosage Forms of Buprenorphine

MEDICATION	DOSAGE FORM(S)	INDICATION	TRADE NAME	COMPANY	STATUS
BUPRENORPHINE ALONE	Injectable Ampules	Pain	<del>BUPRENEX</del> BUPRENEX	Reckitt-Benckiser	Marketed in US
	Injectable Ampules	Pain	Buprenorphine Injectable (generic)	Abbott Laboratories	Marketed in US
	2 or 8 mg Sublingual Tablets	Opioid Dependence	<del>SUBUTEX</del> SUBUTEX	Reckitt-Benckiser	Marketed in US
	0.3 mg Sublingual Tablets	Pain	Buprenorphine Generic s.l. Tablet	Unknown	Marketed in India and other Countries
BUPRENORPHINE/NALOXONE COMBINATION	2 or 8 mg s.l. Tablets with Buprenorphine: Naloxone (4:1)	Opioid Dependence	<del>SUBOXONE</del> SUBOXONE	Reckitt-Benckiser	Marketed in US

# The Science Behind Buprenorphine

---

## Abuse Potential of Buprenorphine Alone (Acute Doses)

*Varies as a function of three factors:*

### 1. Level of physical dependence

- the more dependent, the more likely that BUP will cause precipitated opioid withdrawal

### 2. Time interval between last dose of agonist (e.g., heroin, methadone) and first dose of buprenorphine

- short time interval (< 6 hrs since last agonist) increases the risk of precipitated withdrawal

### 3. Dose of buprenorphine

- lower doses increase risk of precipitated withdrawal

# The Science Behind Buprenorphine

---

## Abuse Potential of Buprenorphine + Naloxone (Acute Doses)

- Naloxone (the antagonist Narcan™) formulated in the Suboxone™ tablet is not readily absorbed sublingually. However, it has good bioavailability if injected. Therefore, if the Suboxone™ tablets are crushed, dissolved and injected, it was predicted that naloxone should produce:
  - blockade of the euphoric & reinforcing effects in non-dependent opioid users. However, this was recently shown not to occur (*Comer et al., 2003*).
  - precipitated withdrawal in opioid-dependent individuals. This does happen.
- Because BUP is a partial *mu*-agonist, it has potential to precipitate withdrawal *by itself* in physically dependent individuals

# The Science Behind Buprenorphine

---

## Effects of Chronic Buprenorphine Administration

- Physical dependence
  - Discontinuation of chronic BUP dosing can result in spontaneous opioid withdrawal signs and symptoms
    - Nausea/vomiting, diarrhea, muscle aches/cramps, insomnia, yawning, sweating, dysphoria, hot/cold feelings, watery eyes/nose, gooseflesh
  - Less severe withdrawal syndrome than with other full agonist opioids (e.g. heroin, methadone)
  - Emergence of withdrawal is delayed (peaks 3-5 days after last dose)
- Minimal effects on other biological or behavioral measures

# The Science Behind Buprenorphine

---

## Types of Clinical Trials

- **Dose-Response**
  - *Schottenfeld et al. (1993); Johnson et al. (1995); Ling et al. (1998)*
  - Moderate to high BUP doses more effective than placebo or low doses
- **Alternate-Day Dosing**
  - *Fudala et al. (1990); Johnson et al. (1995); Amass et al. (1998); Bickel et al. (1999); Petry et al. (1999)*
  - Alternate-day (esp. with double-dose/placebo schedule) equal to every-day
- **Comparisons with Methadone**
  - *Johnson et al. (1992); Strain et al. (1994); Ling et al. (1996); Johnson et al. (2000)*
  - BUP 8 mg/day approximately equal to methadone 60 mg/day

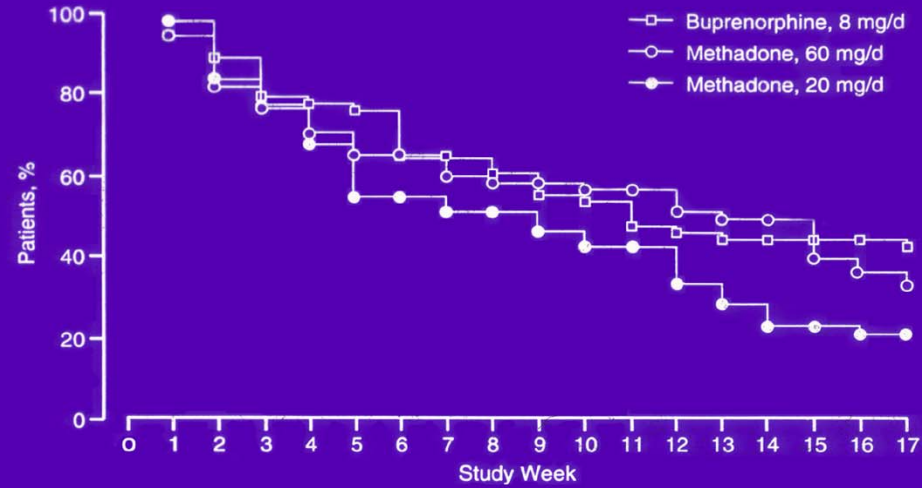


Fig 1.—Patients in each group remaining in treatment at the end of a given week.

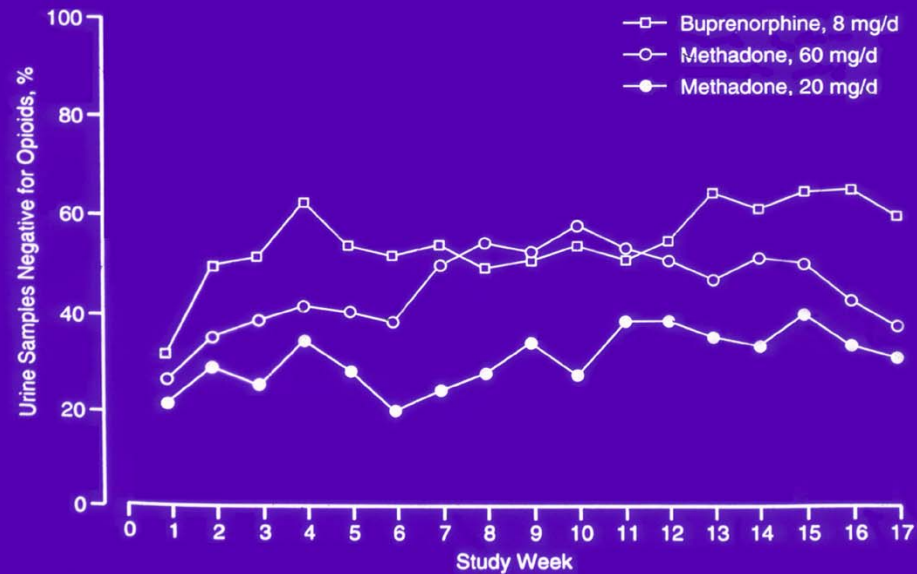
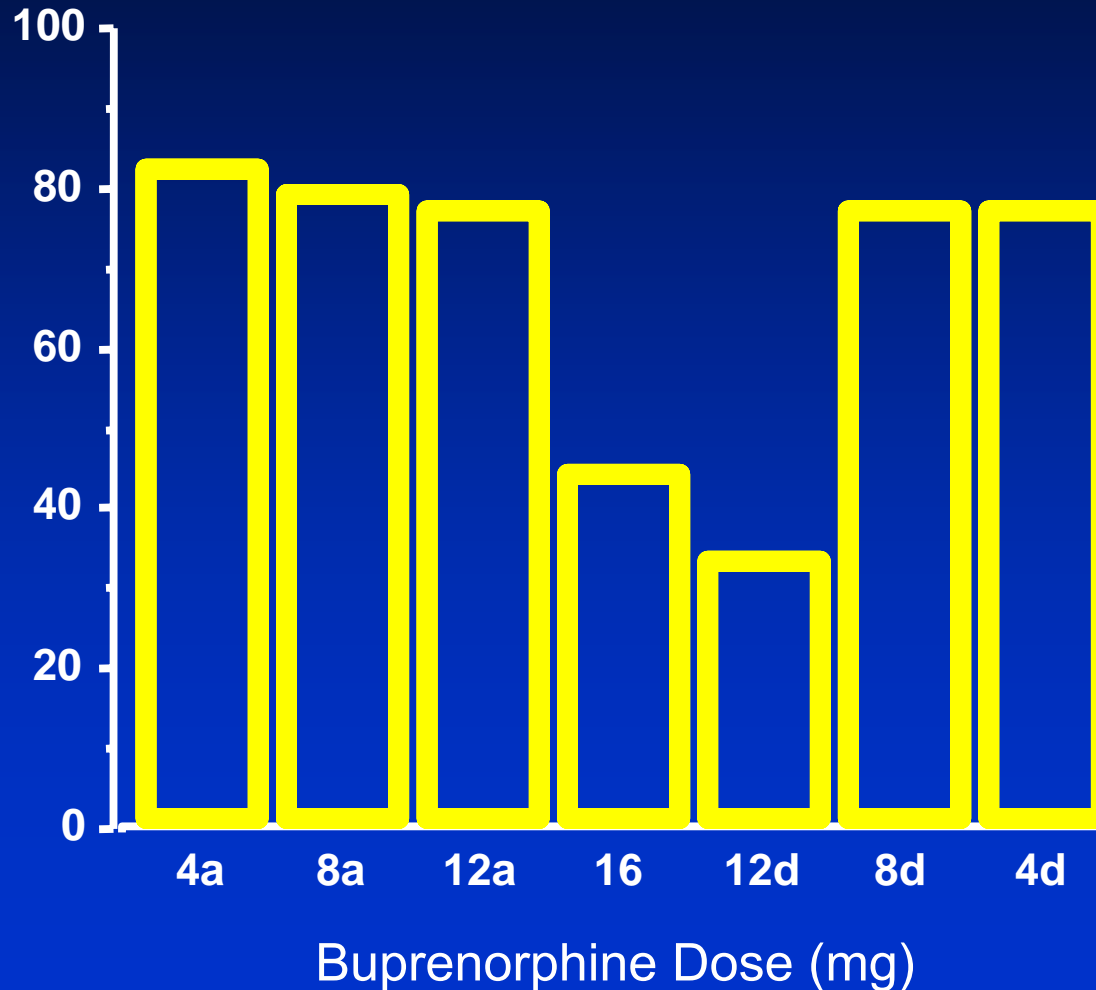


Fig 2.—Urine samples negative for opioids divided by the maximum number of samples that could have been submitted (actually submitted plus missing and considered positive) for each group during a given week.

# The Science Behind Buprenorphine

## % Patients Using Opioids During Buprenorphine Maintenance

*Schottenfeld et al. (1993)*



# The Science Behind Buprenorphine

---

## Multi-Center Randomized Clinical Trial (*Ling et al. 1998*)

- Study Design
  - 239 females and 497 males randomized to 4 dose groups
  - 12 opioid treatment centers throughout U.S.
  - Patients received 1,4,8, or 16mg/day BUP (s.l. liquid)
  - Four outcome domains
    - retention, urine toxicology, craving, global ratings (by patients and staff)
- Main Findings
  - Outcomes in 8 and 16 mg groups significantly better than 1 mg group (16 mg n.s. better than 8 mg)
  - No significant increase in adverse events at higher doses

# The Science Behind Buprenorphine

Ling et al. (1998)

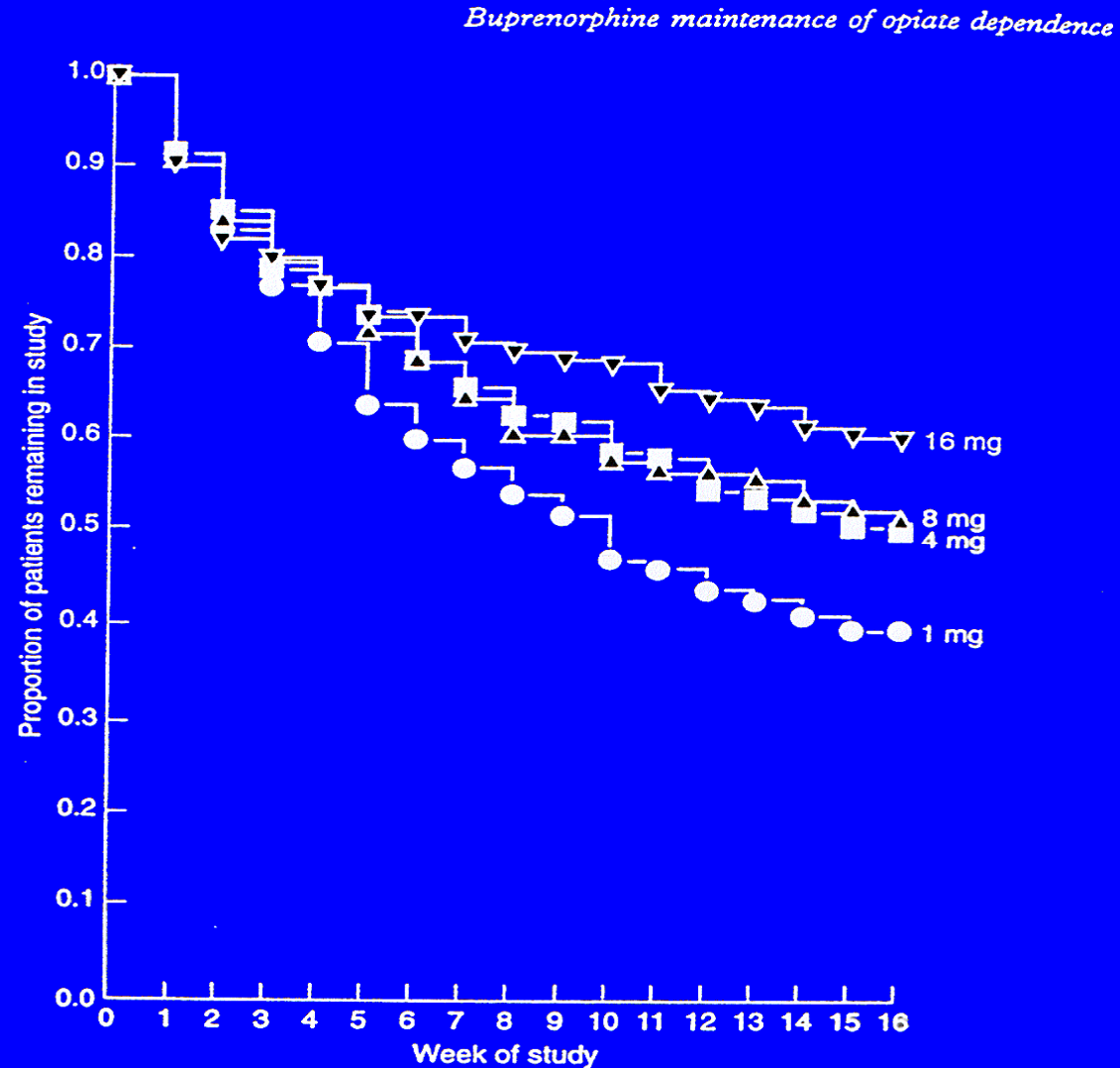


Figure 1. Proportion of patients in each dosage group still in treatment by week.

# The Science Behind Buprenorphine

---

## Summary of Buprenorphine Clinical Trial Data

- BUP is effective for opioid maintenance treatment in randomized, controlled clinical trials
- Alternate-day dosing is effective and feasible
- Side effect profile appears milder than with other opioid agonists
  - No clinically significant constipation, psychomotor disruption, or medical problems (e.g. liver toxicity)
  - No overdoses, but need to be aware of interaction with sedatives that can potentiate respiratory depression
- Not as well studied, but BUP may also provide a more comfortable (tolerable) method of detoxification
- Suboxone™ likely to have low abuse potential (being evaluated in Phase IV surveillance studies)

# Clinical Practice with Buprenorphine

---

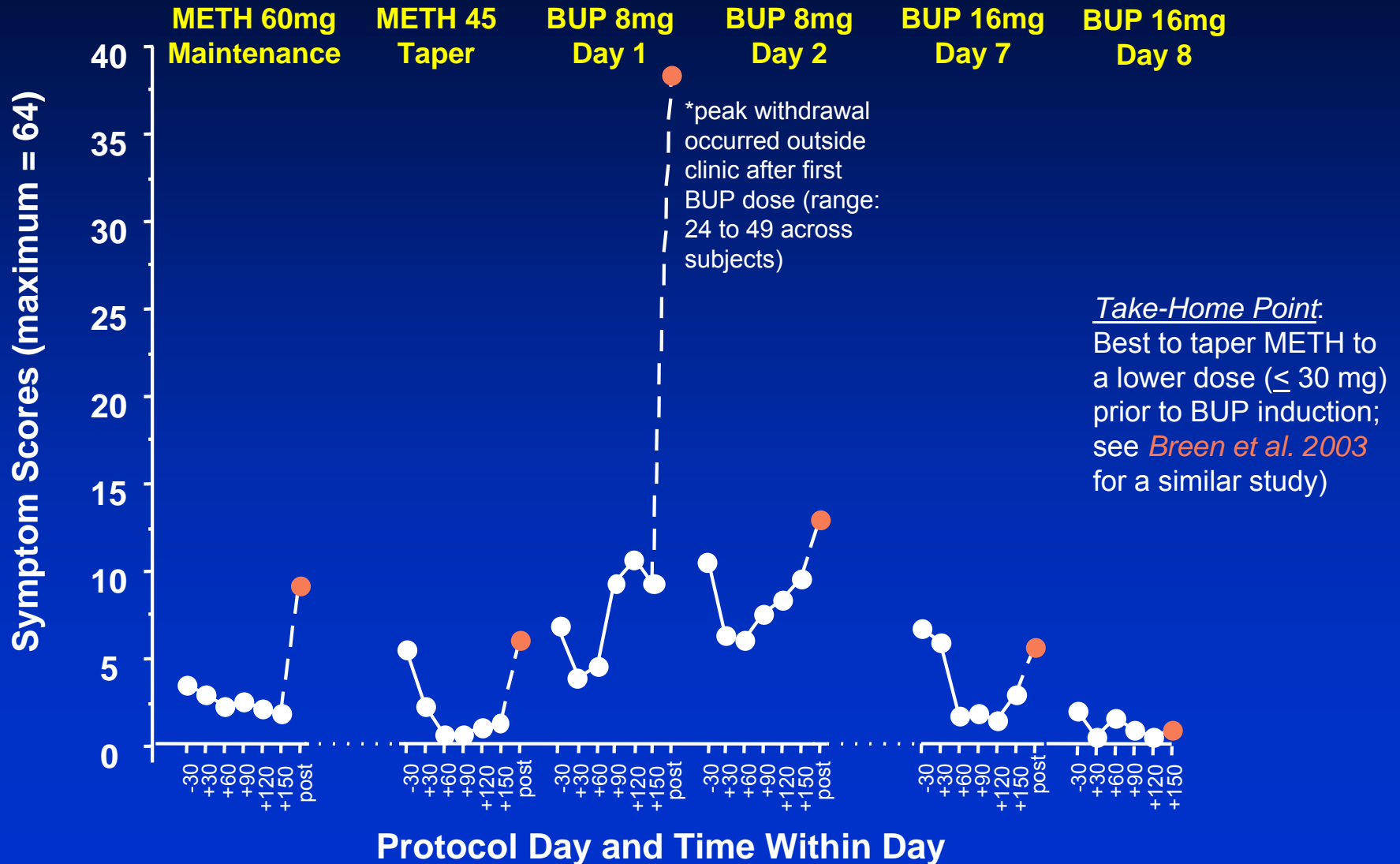
## Buprenorphine Treatment: How it Works (1)

- *Induction*

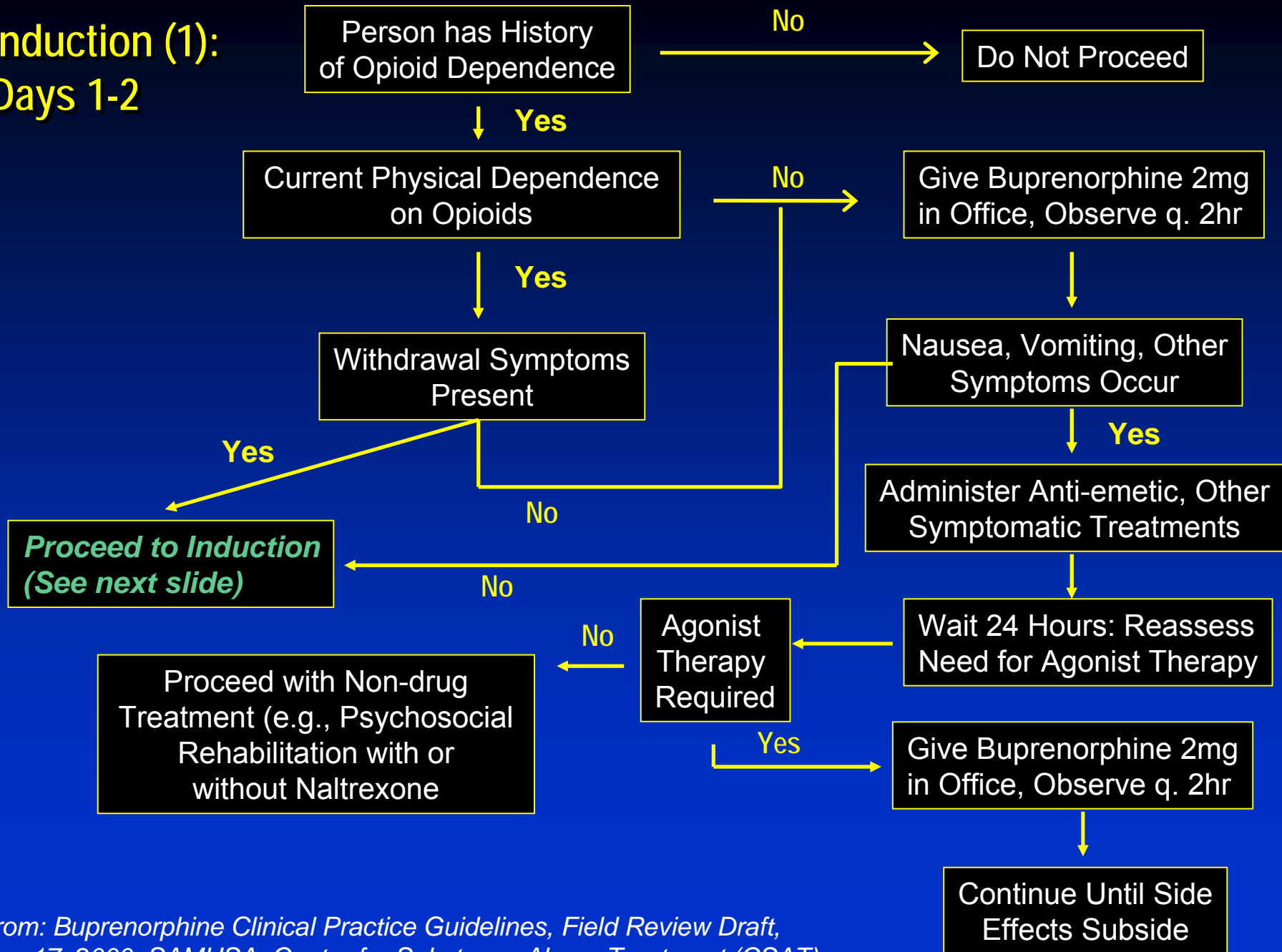
- Psychological evaluation prior to induction
  - Any contraindications? (e.g. mental health problem or anxious response to opioid withdrawal)
- When to administer BUP and what dose? Consider whether patient:
  - Is dependent on a short acting opioid (e.g. heroin) or a long acting opioid (e.g. methadone); trickier if long-acting
  - Is already experiencing spontaneous opioid withdrawal (*i.e.* time since taking last opioid dose). Ideally, patient should be in mild withdrawal so that BUP suppresses these effects (*i.e.* associate BUP with opioid withdrawal relief)
- Post-induction monitoring
  - Keep patient in office for several hours for observation
  - May administer additional BUP doses if needed (10 mg max. on day 1)

# Clinical Practice with Buprenorphine

## Withdrawal During Methadone-to-BUP Transition (*Greenwald et al. 2003*)

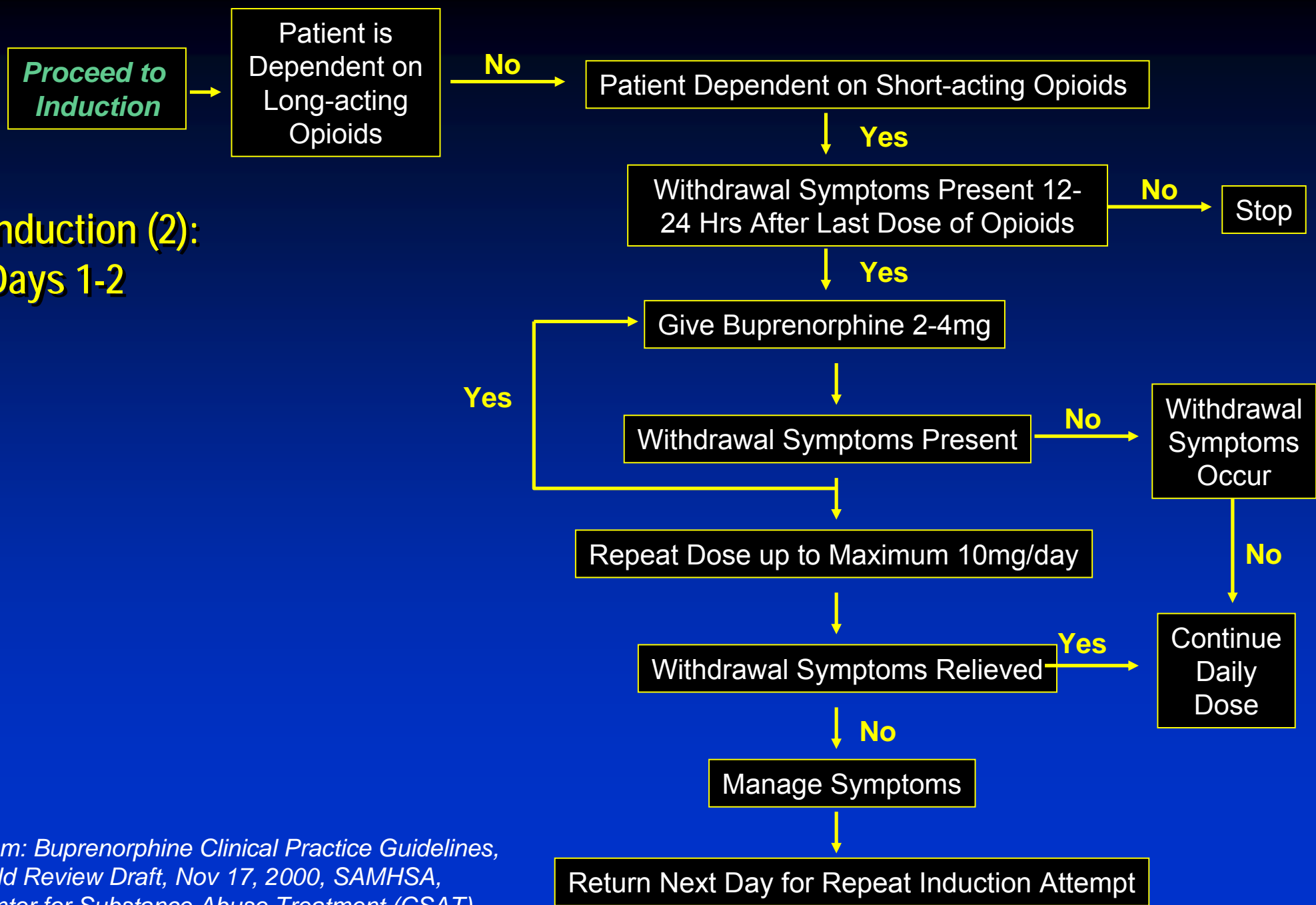


# Induction (1): Days 1-2



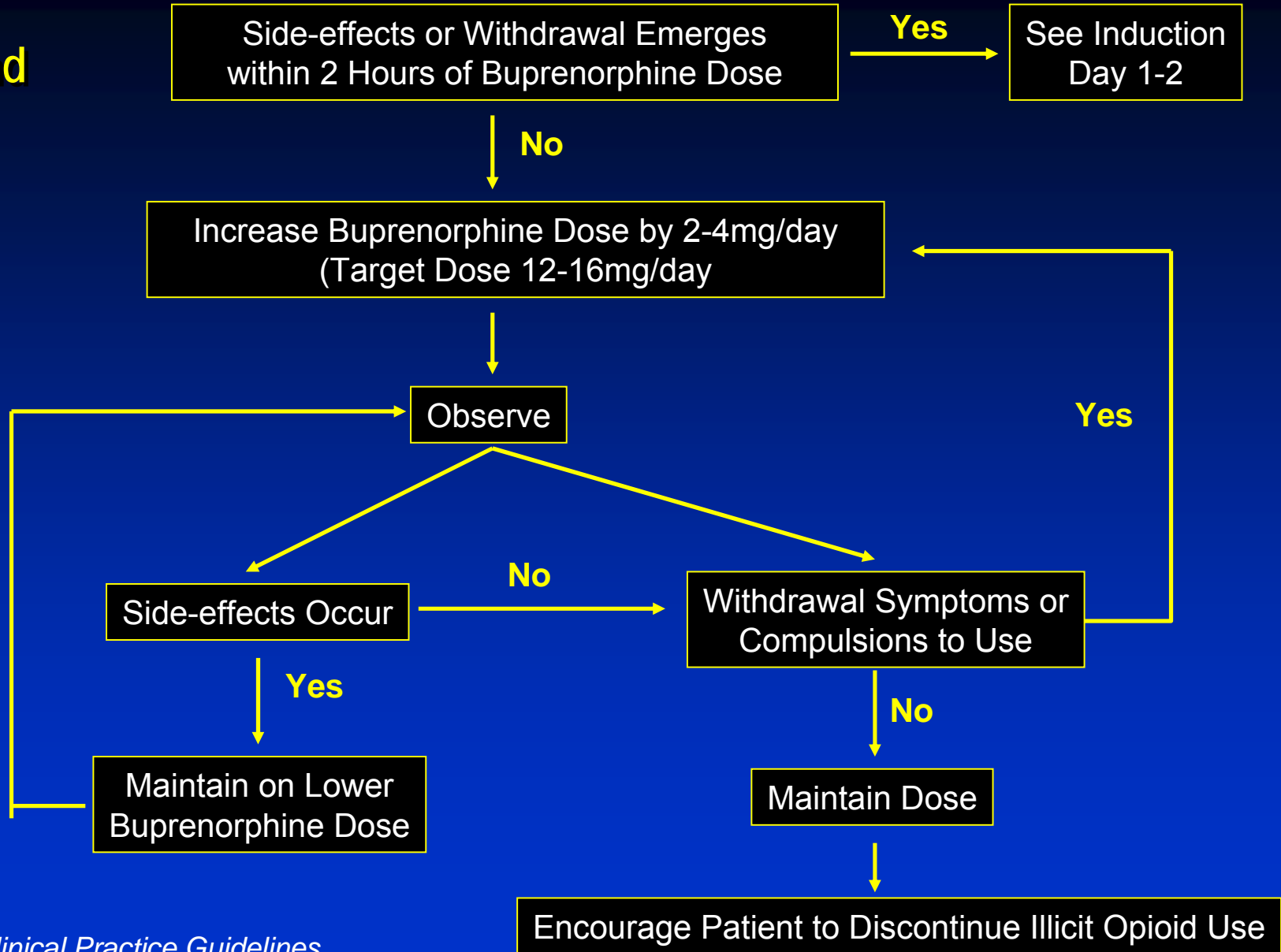
From: Buprenorphine Clinical Practice Guidelines, Field Review Draft, Nov 17, 2000, SAMHSA, Center for Substance Abuse Treatment (CSAT)

**Induction (2):  
Days 1-2**



*From: Buprenorphine Clinical Practice Guidelines, Field Review Draft, Nov 17, 2000, SAMHSA, Center for Substance Abuse Treatment (CSAT)*

## Induction (3): Day 2 & Beyond



*From: Buprenorphine Clinical Practice Guidelines,  
Field Review Draft, Nov 17, 2000, SAMHSA,  
Center for Substance Abuse Treatment (CSAT)*

# Clinical Practice with Buprenorphine

---

## Buprenorphine Treatment: How it Works (2)

- *Maintenance*
  - Stabilize on daily dose that prevents withdrawal and, with the addition of other psychological treatment, promotes cessation of illicit opioid use
    - Wide individual differences; because BUP is a partial agonist, some patients may require high doses, but there are no safety concerns with doing this
  - Once stabilized, consider alternate-day dosing (M-W-F or even M-Th):
    - Decision can be based on convenience for the patient (*e.g.* distance from clinic) or needs of the clinic (*e.g.* limited staff resources)
    - Use alternate-day BUP dosing as a privilege, *i.e.* to reinforce continuous opioid abstinence (based on urine results) – 'graduation' from every-day dosing
    - Take-home privileges may add potency and cost-effectiveness to treatment
  - Most important time for psychological intervention (*i.e.* patient and family more receptive when comfortable)

# Clinical Practice with Buprenorphine

---

## Buprenorphine Treatment: How it Works (3)

- *Detoxification*

- Depends on level of physical dependence
  - Higher BUP maintenance doses ( $\geq 12$  mg) will take longer to achieve a more comfortable detoxification
- Depends on the context
  - Can rapidly taper the dose over a few days (e.g. with clonidine and transition to naltrexone); often done while inpatient but also outpatient
  - Gradual outpatient dose-taper over several weeks
- Psychologists can help patients prepare for, and response to problems during, detoxification (e.g. relapse prevention)

# Clinical Practice with Buprenorphine

---

## Buprenorphine Treatment: Summary

- **Buprenorphine works**
  - Maintains clinic attendance, enabling combination treatment that reduces harms of illicit drug use and promotes pro-social activities
  - At adequate doses, equivalent to methadone and LAAM in effectiveness, and:
    - Safer than either
    - Longer-acting than methadone
    - Accessibility in private practice
- **Psychologists are an important part of the treatment team**
  - Assessment prior to BUP induction
  - Intervention on multiple levels during maintenance
  - Relapse prevention during maintenance and detoxification