

**Buprenorphine:
A New Medication for the Treatment of Opioid
Dependence**

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Basic Pharmacology: Buprenorphine

Overview

Buprenorphine a thebaine derivative

High potency

Available as a parenteral analgesic

Produces sufficient agonist effects to be detected by the patient

Used outside United States for the treatment of opioid dependence

Buprenorphine

- Buprenorphine is a partial agonist of the μ -opioid receptor.
- At low doses, it behaves as an agonist; at high doses or in patients dependent on high doses of chronic opioids, it has the ability to act as an antagonist.

Affinity and Dissociation

Buprenorphine has:

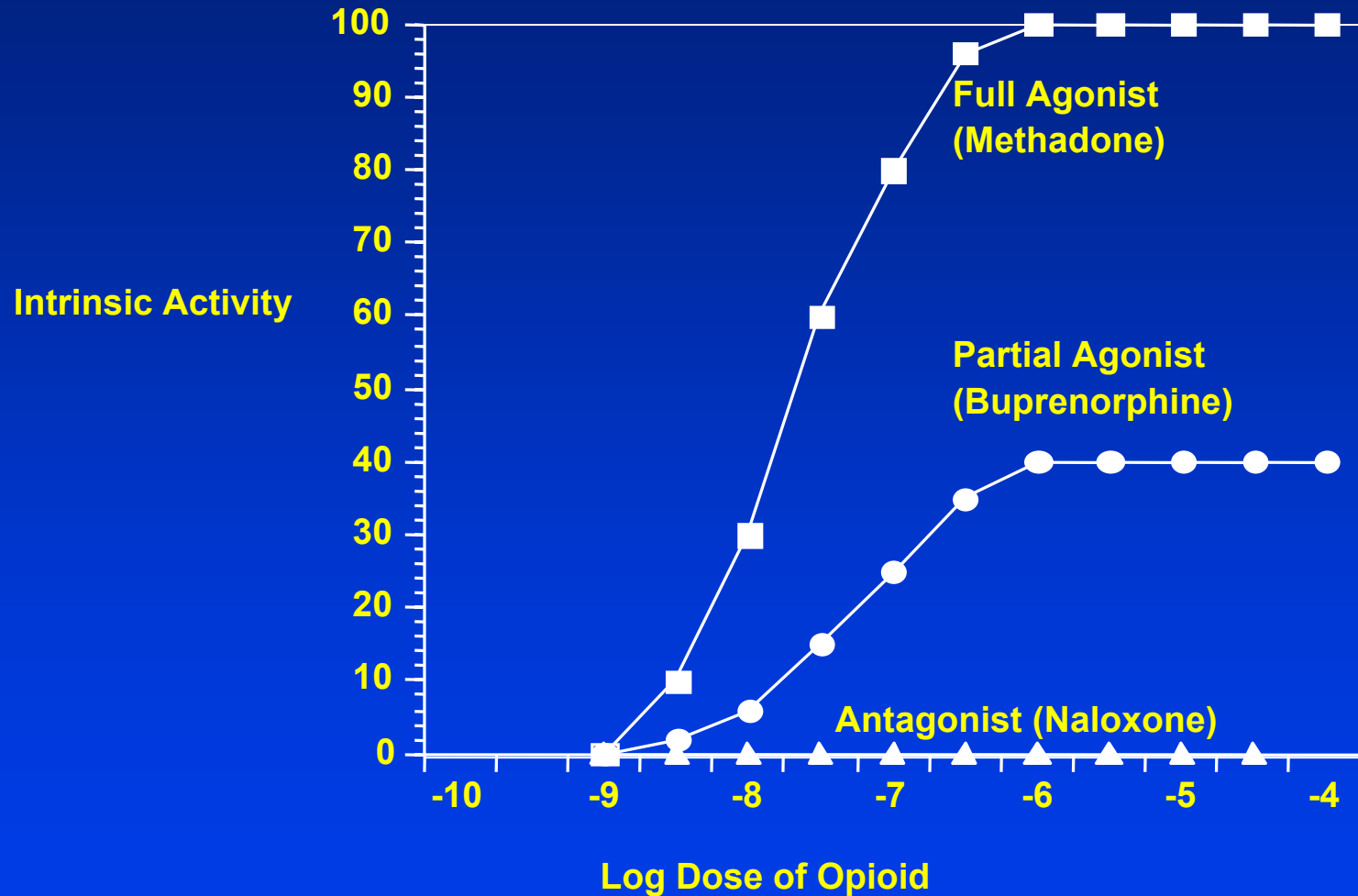
high affinity for mu opioid receptor –

competes with other opioids and blocks their effects

slow dissociation from mu opioid receptor –

prolonged therapeutic effect for opioid dependence treatment

Intrinsic Activity: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



Bioavailability

Good parenteral bioavailability

Poor oral bioavailability

Fair sublingual bioavailability

For opioid dependence treatment:

early clinical trials used an alcohol-based solution

FDA approval for tablets that are held under tongue

Abuse Potential

Buprenorphine is abusable (epidemiological, human laboratory studies show)

Diversion and illicit use of analgesic form (by injection)

Relatively low abuse potential compared to other opioids

Abuse Potential

Human laboratory studies of abuse liability in two populations:

Non-dependent opioid users

Physically dependent opioid users

Abuse Potential

Non-dependent opioid user

Single doses of buprenorphine produce typical mu agonist effects

shown when given by injection and sublingual route

Onset of effects slower for sublingual route (suggesting lower abuse potential)

Abuse Potential

Physically dependent opioid user

Abuse potential of buprenorphine varies as function of three factors:

level of physical dependence

time interval between last dose of agonist and first dose of administered buprenorphine

dose of buprenorphine

Abuse Potential

Level of physical dependence

The higher the level of physical dependence, the greater chance of precipitated withdrawal

For example:

With maintenance on 60 mg/day of methadone – precipitated withdrawal seen with single doses of sublingual buprenorphine

With maintenance on ≤ 30 mg/day methadone – markedly decreased risk of precipitated withdrawal with buprenorphine

Abuse Potential

Time interval

At short time intervals (e.g., 2 hours after a dose of methadone), increased likelihood of buprenorphine precipitated withdrawal

At longer time intervals, more likely buprenorphine is either placebo-like or opioid agonist-like

Abuse Potential

Dose of buprenorphine

Low single doses of buprenorphine given acutely produce minimal effects (e.g., placebo-like or opioid agonist-like)

Higher doses can precipitate withdrawal in persons physically dependent on opioids

Potential for Physical Dependence

Repeated administration of buprenorphine produces or maintains physical dependence

However, degree of physical dependence is less than that produced by full agonist opioids

This means withdrawal syndrome should be less severe for buprenorphine

Sublingual Naloxone

Sublingual naloxone has relatively poor bioavailability

Dose up to 1-2 mg sublingual do not precipitate withdrawal
in opioid dependent volunteers

Sublingual naloxone does have a bitter taste

Combination of Buprenorphine plus Naloxone

Sublingual buprenorphine has fair bioavailability

Addition of naloxone to buprenorphine to decrease abuse potential of tablets

Combination ratio is 4 to 1 (buprenorphine to naloxone)

Combination of Buprenorphine plus Naloxone

Combination tablet containing buprenorphine with naloxone
– if taken under tongue, predominant buprenorphine effect

If opioid dependent person dissolves and injects buprenorphine/naloxone tablet – predominant naloxone effect (and precipitated withdrawal)

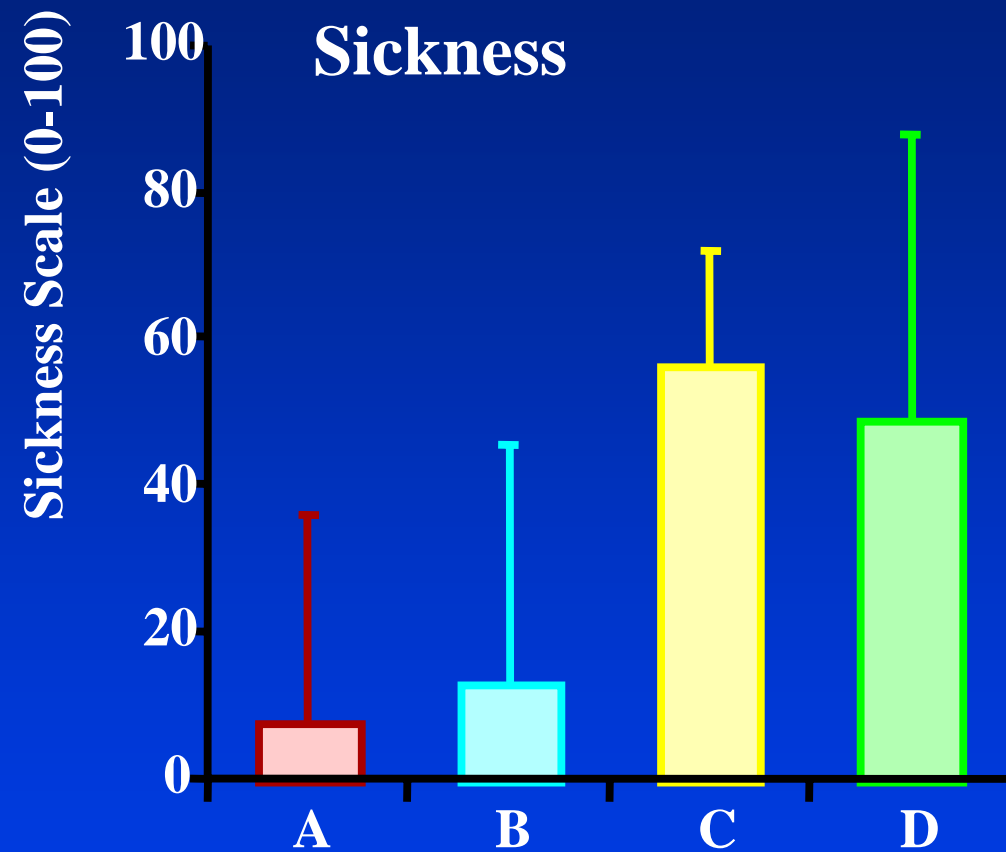
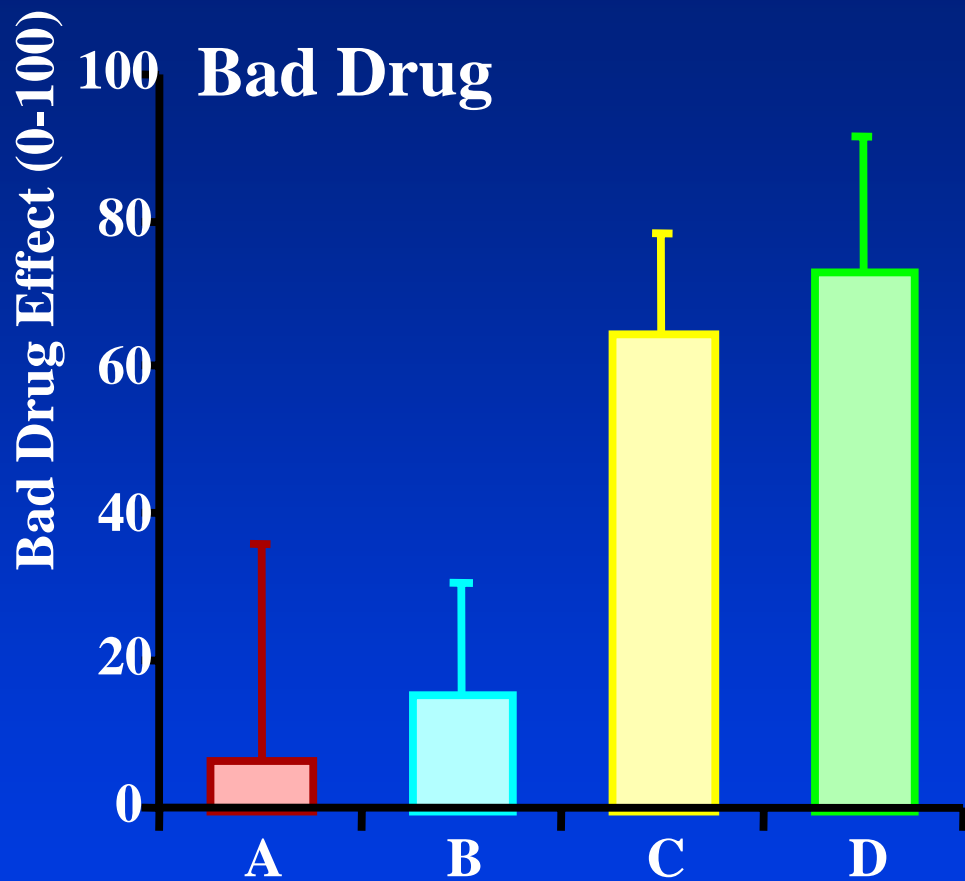
Rationale for Buprenorphine/naloxone

- When taken sublingually
 - Buprenorphine will be well absorbed
 - Naloxone absorption will be minimal
- If taken intravenously
 - Naloxone 100% bioavailable
 - Precipitated withdrawal occurs in opioid maintained patients

Buprenorphine/naloxone infusion

- Study on methadone maintained patients (Mendelson)
- Looked at 6 patients on stable methadone doses of 45 to 60 mg/day
- Challenged IV with
 - Buprenorphine 0.2 mg
 - Naloxone 0.1 mg
 - Buprenorphine 0.2 and Naloxone 0.1 mg
 - Placebo

PEAK EFFECTS – MEAN (\pm SD)



A Buprenorphine placebo, Naloxone placebo

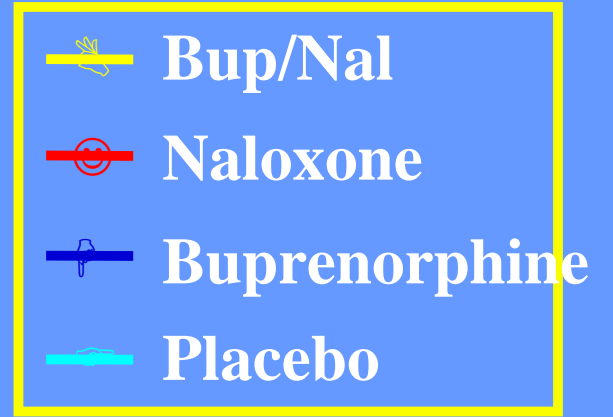
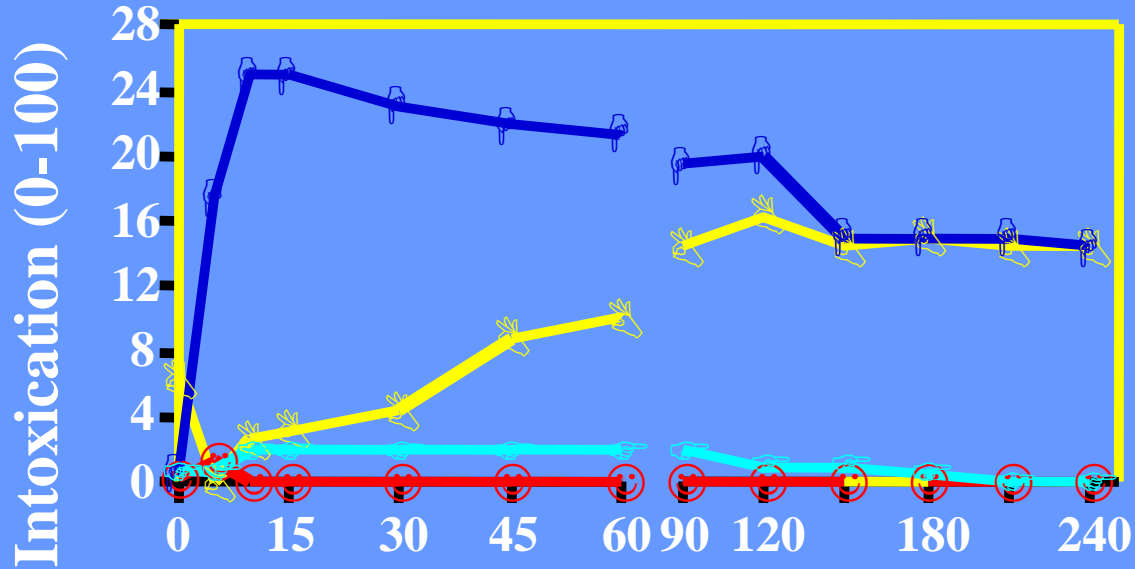
B Buprenorphine 0.2 mg, Naloxone placebo

C Buprenorphine placebo, Naloxone 0.1 mg

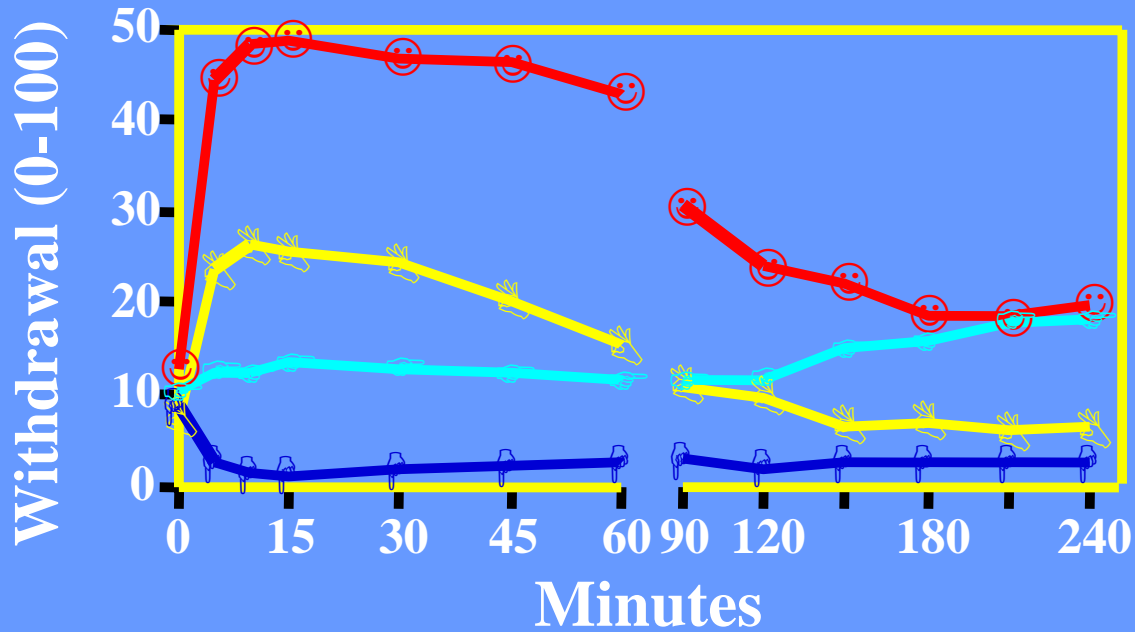
D Buprenorphine 0.2 mg, Naloxone 0.1 mg

Clinical Implications

- Buprenorphine produced only minimal opiate agonist effects
- A small dose of naloxone is highly aversive in this population
- The buprenorphine/naloxone combination behaves like naloxone
- Abuse potential of buprenorphine/naloxone probably very low in methadone maintained patients



**Mean Peak Amount
Would Pay for Drug**



Bup/Nal	\$ 1.90 ± 3.70
Naloxone	0.00 ± 0.00
Buprenorphine	11.90 ± 7.00
Placebo	0.00 ± 0.00

Clinical Implications

- Buprenorphine mono product produces pleasurable effects and would be purchased by illicit drug users
- Naloxone when combined with buprenorphine attenuates euphoric effects
- Buprenorphine/naloxone should decrease abuse liability in untreated opioid dependent individuals

Efficacy of Buprenorphine

Maintenance treatment using buprenorphine

Medically-managed withdrawal using buprenorphine

Maintenance Treatment Using Buprenorphine

Numerous outpatient clinical trials comparing efficacy of daily buprenorphine to placebo, and to methadone.

Maintenance Treatment Using Buprenorphine

These studies conclude:

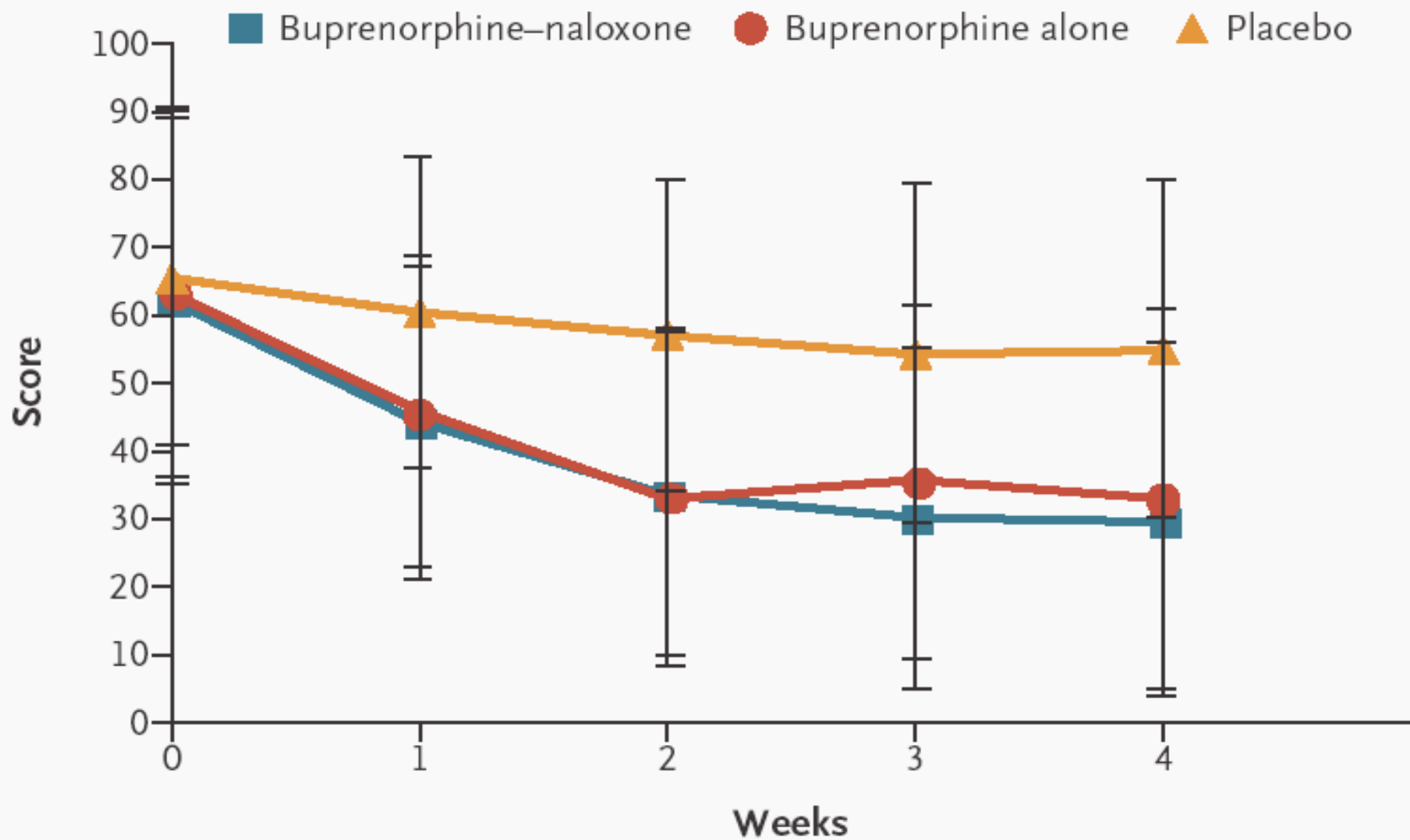
Buprenorphine more effective than placebo

Buprenorphine equally effective as moderate doses of methadone (e.g., 60 mg per day)

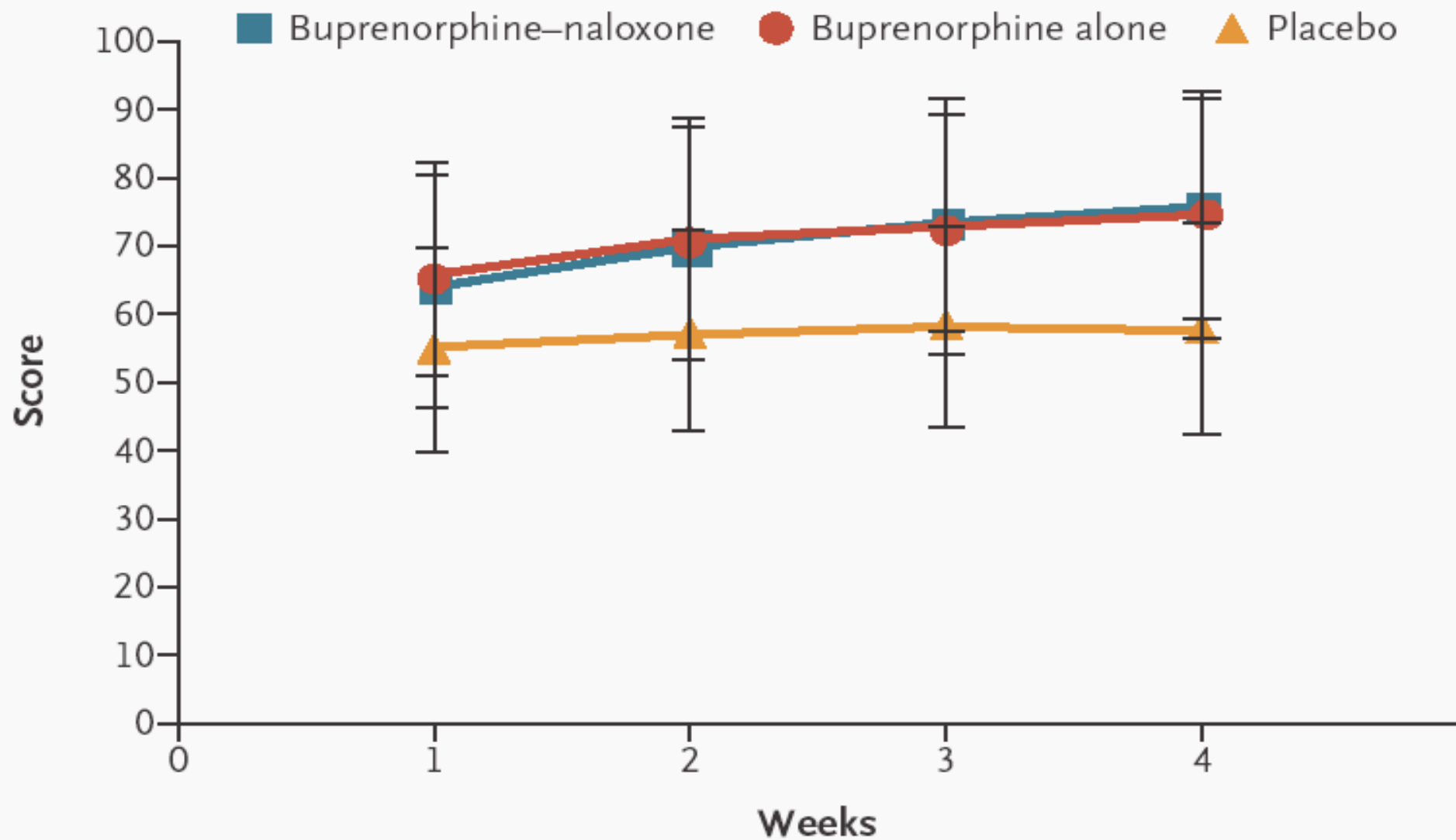
Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone

- Fudala, et al, NEJM 2003; 349:949-58
- Multi-center, 2 phase study
 - 3-Arm random assignment: Buprenorphine, Buprenorphine/Naloxone or Placebo x 28 days, (n=326)
 - Open-label Buprenorphine/Naloxone for up to 11 months, if in above arm , or 12 months if not (n=461)

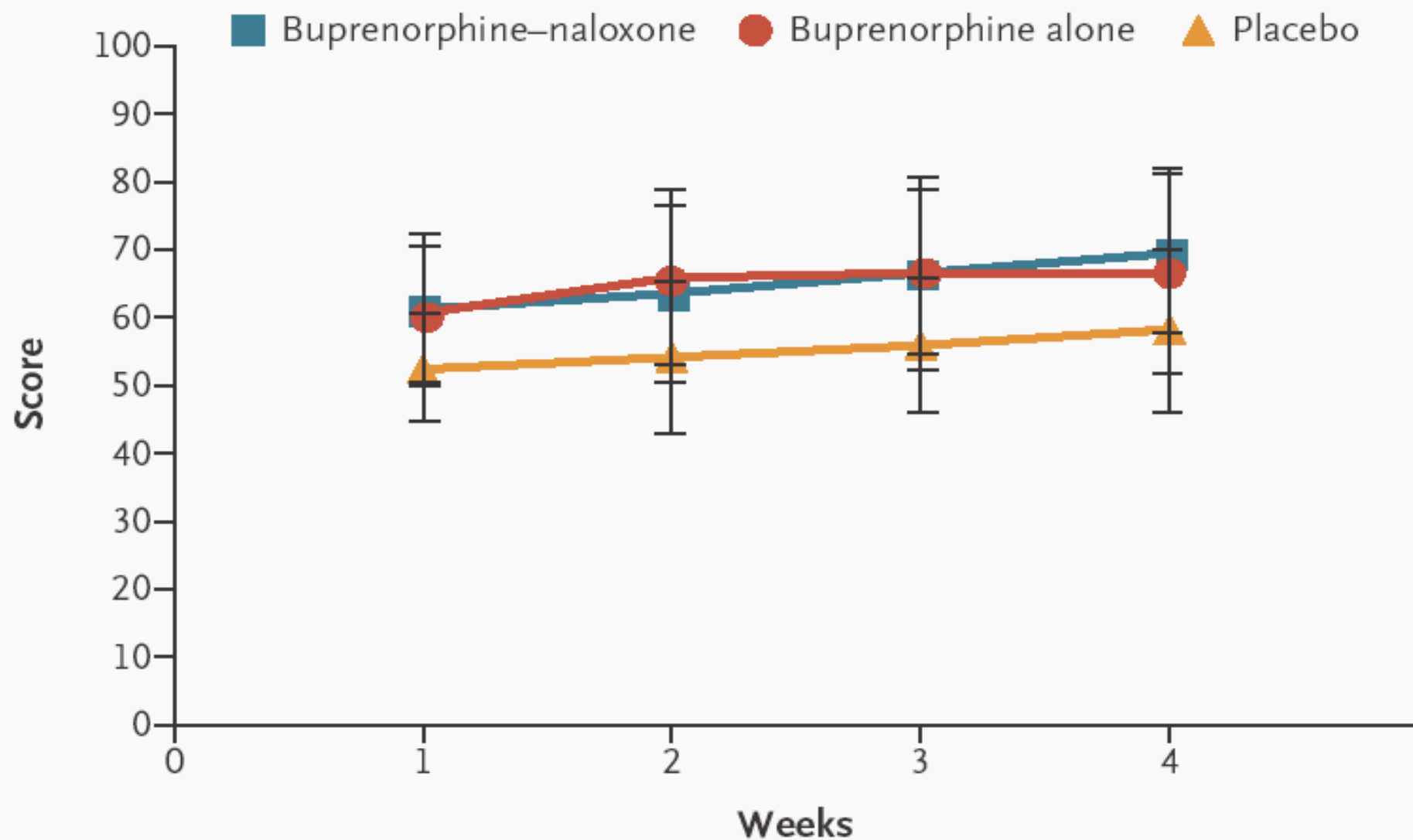
A Opiate Craving

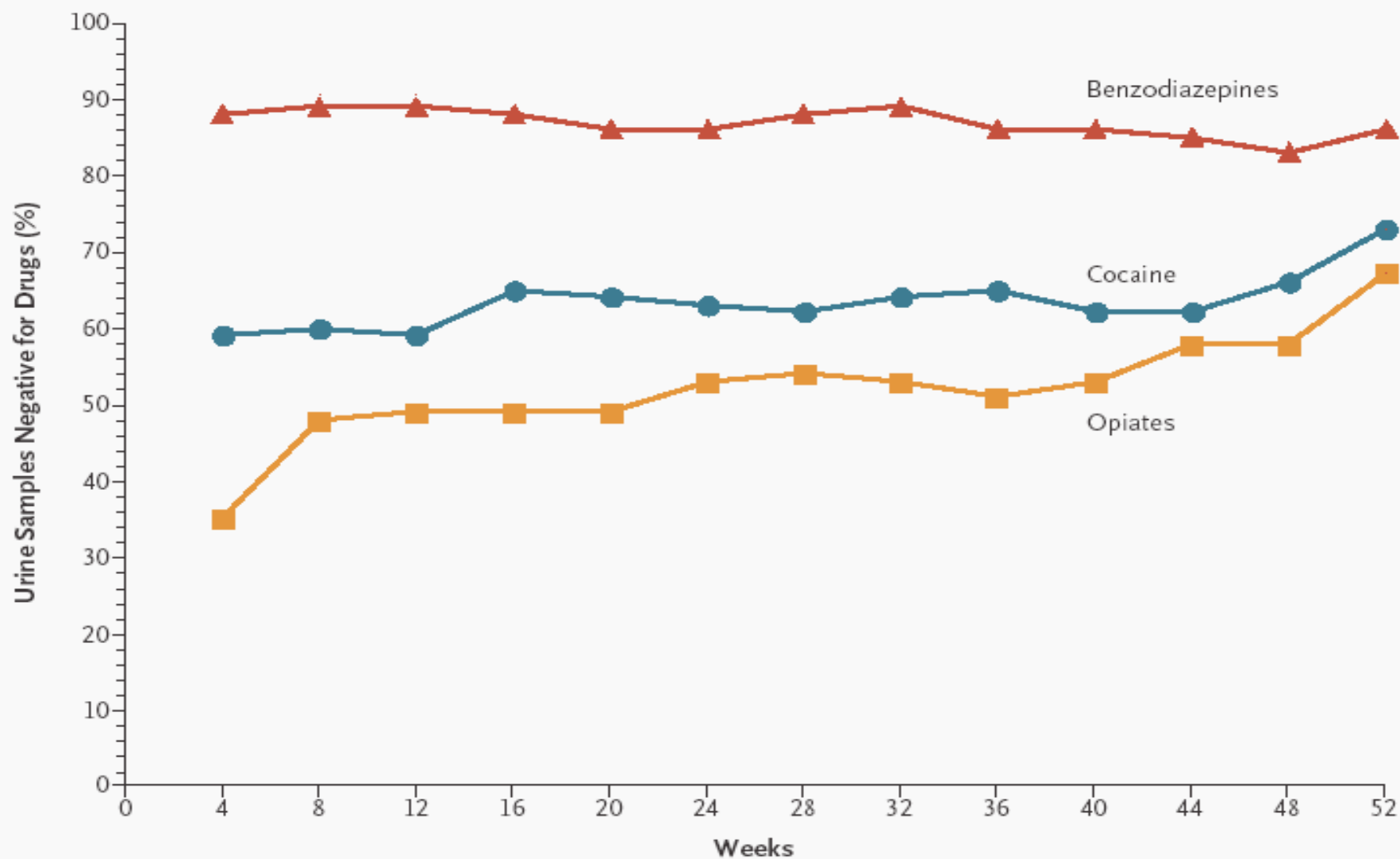


B Subjects' Impression of Overall Status



C Clinicians' Impression of Overall Status

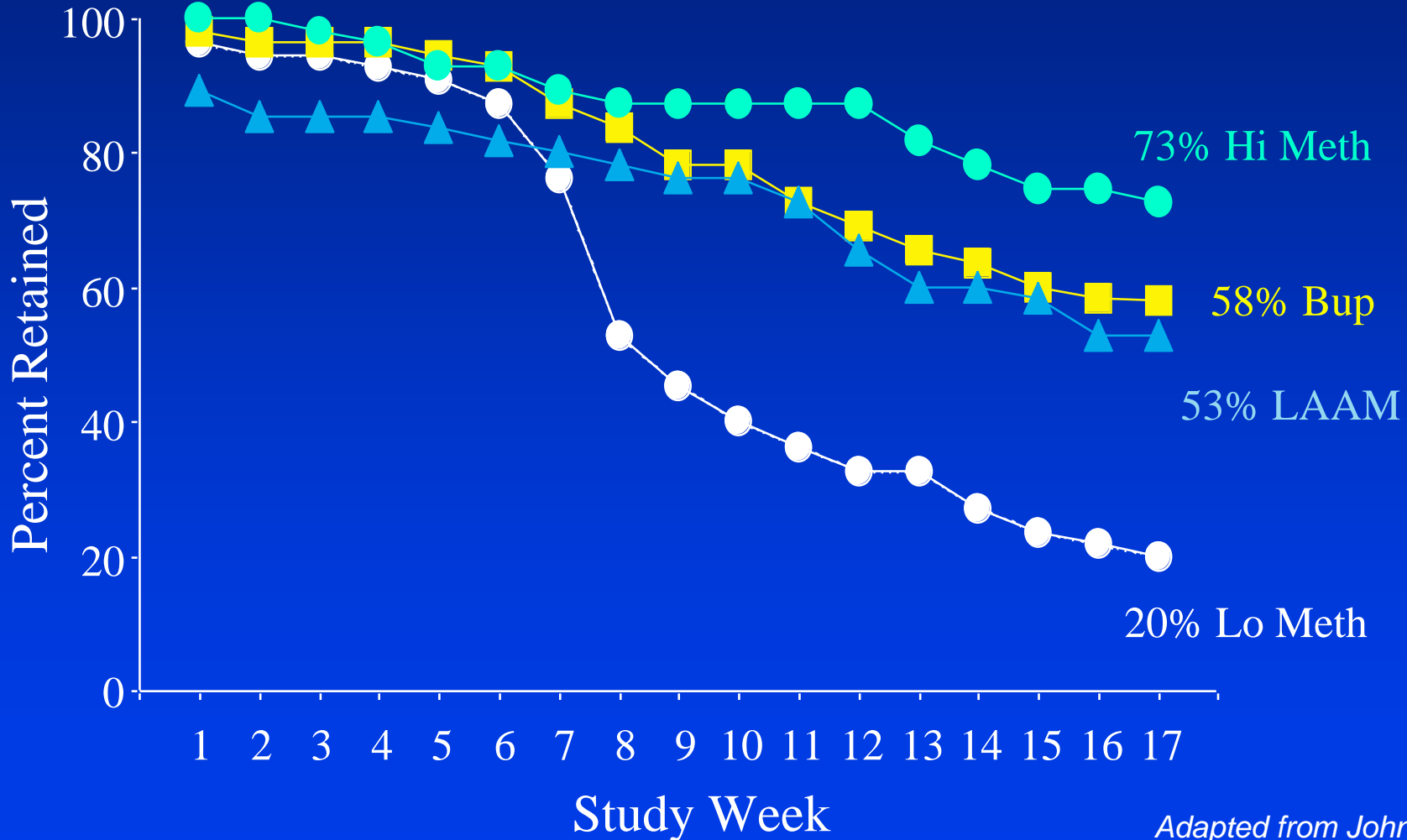




No. of Samples Tested

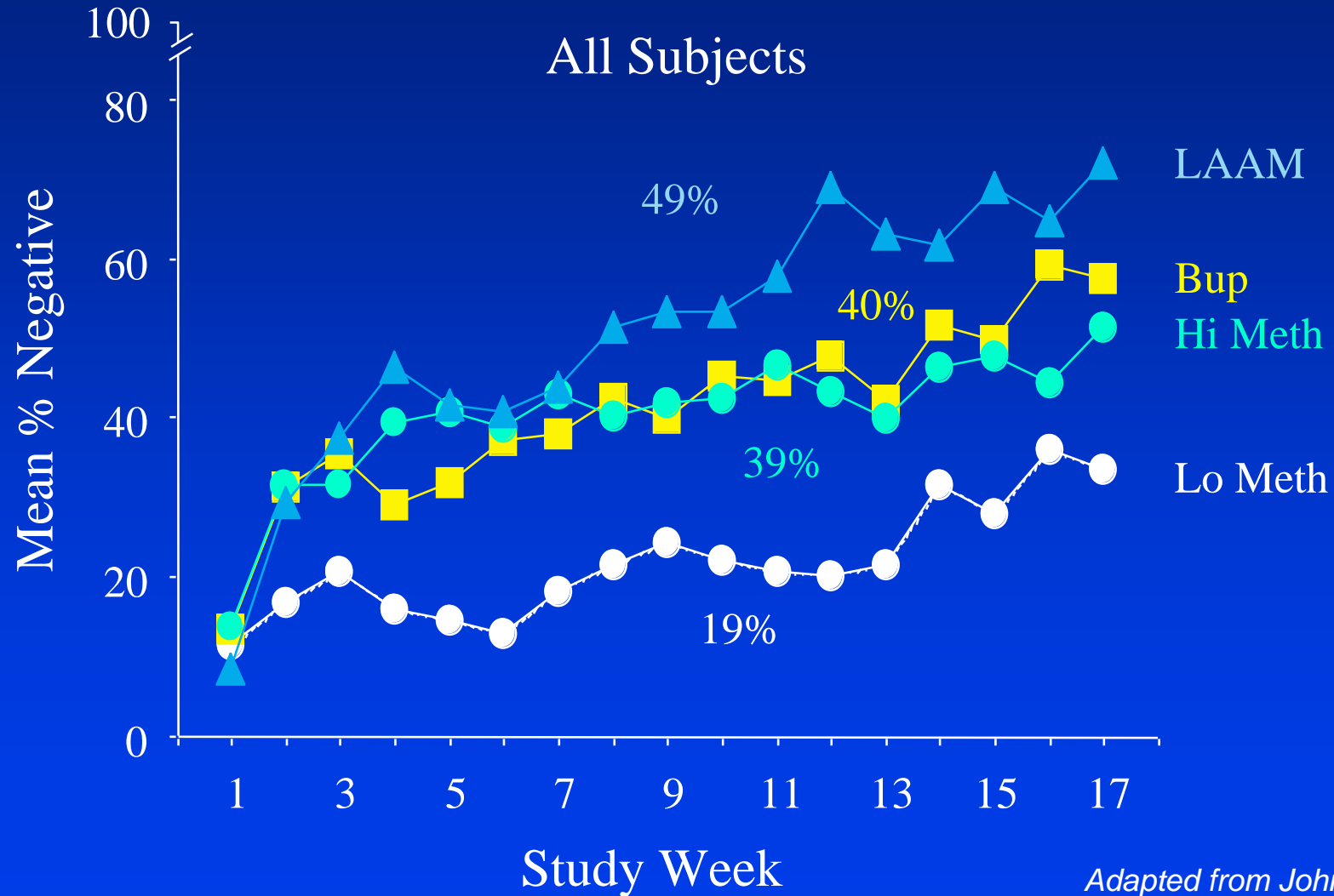
For cocaine or benzodiazepines	824	667	632	563	537	494	448	449	408	383	361	323	178
For opiates	943	675	633	564	537	494	449	449	408	383	361	323	178

Buprenorphine, Methadone, LAAM: Treatment Retention



Adapted from Johnson, et al., 2000

Buprenorphine, Methadone, LAAM: Opioid Urine Results



Adapted from Johnson, et al., 2000

Overview to Safety

Highly safe medication (acute and chronic dosing)

Primary side effects: like other mu agonist opioids (e.g., nausea, constipation), but may be less severe

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

No evidence of organ damage with chronic dosing

Teratogenesis

Limited information about use of buprenorphine in pregnant, opioid dependent women

No reports of teratogenic effects (but limited number of cases)

Review of buprenorphine use in pregnancy in Special Populations lecture

Precipitated Withdrawal

Reviewed in Basic Pharmacology section

Buprenorphine-precipitated withdrawal seen in controlled studies has been mild in intensity and of short duration

Overdose with Buprenorphine

Low risk of clinically significant problems

No reports of respiratory depression in clinical trials comparing buprenorphine to methadone

Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression or other significant problems

Overdose of buprenorphine combined with other drugs may cause problems (reviewed below)

Benzodiazepines and Other Sedating Drugs

Reports of deaths when buprenorphine injected along with benzodiazepines

Reported from France, where tablets available – appears patients dissolve and inject tablets

Probably possible for this to occur with other sedatives as well

Appropriateness for Office-based Buprenorphine

- Consider these factors
 1. Does the patient have a diagnosis of opioid dependence?
 2. Is the patient interested in office-based buprenorphine treatment?
 3. Does the patient understand the risks/benefits of buprenorphine treatment?

Appropriateness for Office-based Buprenorphine

- Consider these factors (continued)
 4. Is he/she expected to be reasonably compliant?
 5. Is he/she expected to follow safety procedures?
 6. Is the patient psychiatrically stable?

Appropriateness for Office-based Buprenorphine

- Consider these factors (continued)
 7. Are the psychosocial circumstances of the patient stable and supportive?
 8. Can the office provide the needed resources for the patient (either on or off site)?
 9. Is the patient taking other medications that may interact with buprenorphine?

Appropriateness for Office-based Buprenorphine

Patient is less likely to be an appropriate candidate for office-based buprenorphine treatment

1. Dependence on high doses of benzodiazepines, alcohol, or other CNS depressants
2. Significant psychiatric co-morbidity
3. Active or chronic suicidal or homicidal ideation or attempts

Appropriateness for Office-based Buprenorphine

Patient is less likely to be an appropriate candidate for office-based buprenorphine treatment (continued)

4. Multiple previous treatments and relapses
5. Non-response to buprenorphine in the past
6. High level of physical dependence (risk for severe withdrawal)
7. Patient needs cannot be addressed with existing office-based resources

Appropriateness for Office-based Buprenorphine

Patient is less likely to be an appropriate candidate for office-based buprenorphine treatment (continued)

8. High risk for relapse

9. Pregnancy

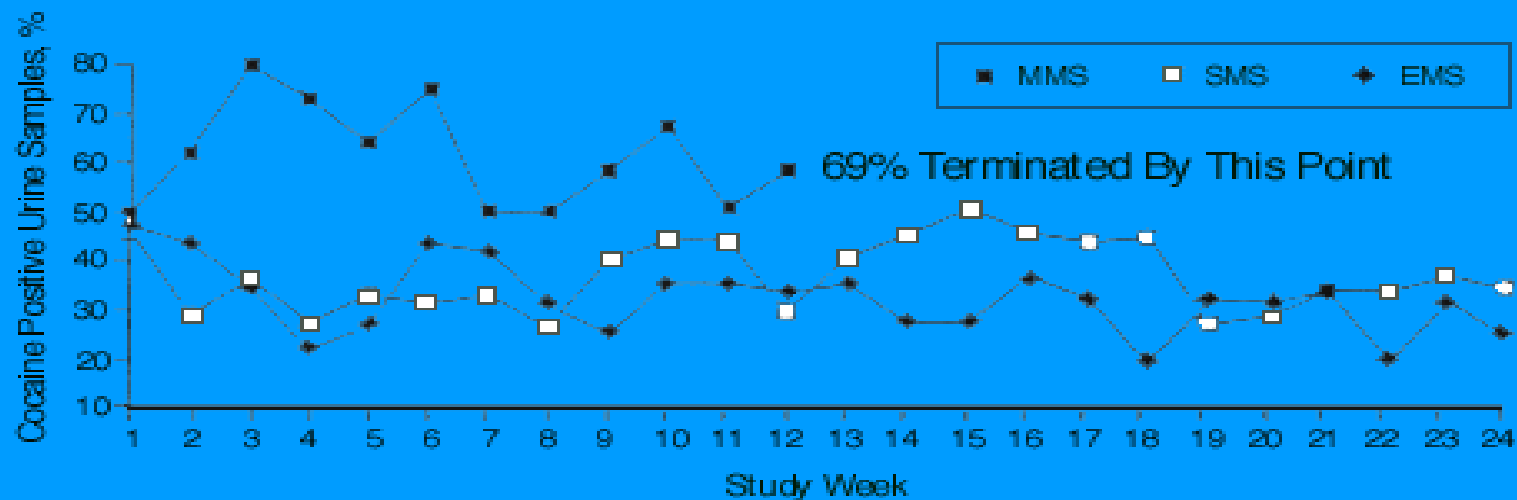
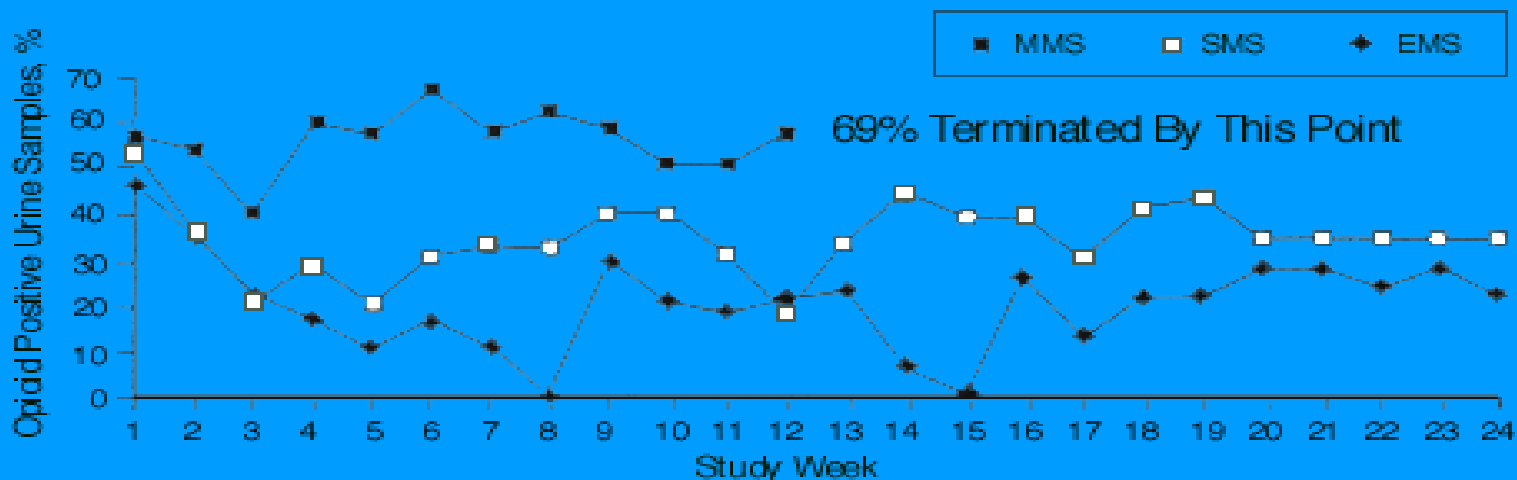
10. Current medical condition(s) that could complicate treatment

11. Poor support systems

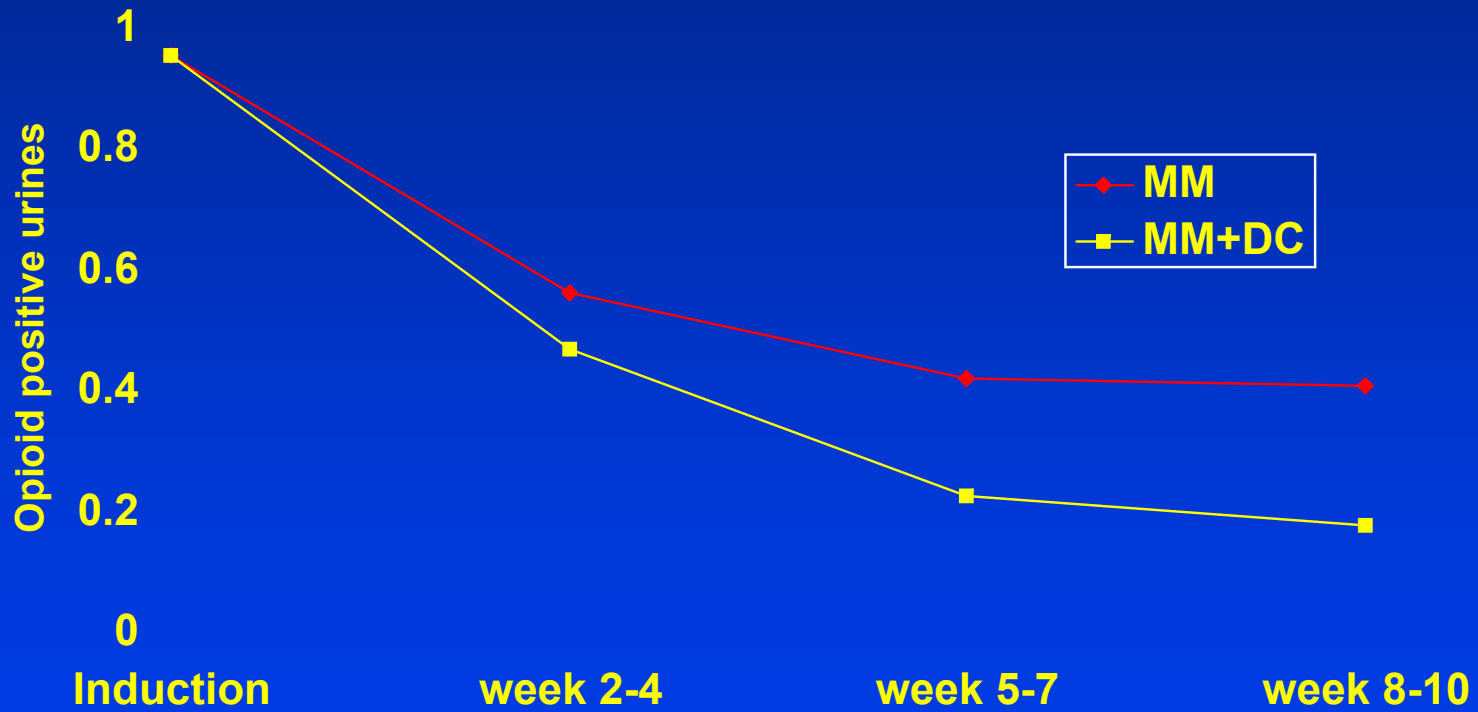
Evidence for psychosocial counseling

- The “dose” of these services can determine treatment outcomes
- McLellan et al., 1993:
 - 6-month randomized clinical trial
 - three levels of psychological services
 - methadone alone
 - methadone plus standard counseling services
 - methadone plus enhanced services (counseling, medical/psychiatric, employment, and family therapy)

Effect of Counseling in Methadone Treatment



Effect of counseling in buprenorphine treatment (Fiellin, 2002)



Preparation for Induction

- Are all necessary assessments completed?
 - H & P
 - ECG
 - Labs
 - Psychosocial assessment
 - Consent for treatment and, If necessary, treatment contract
- Is patient education for induction completed?

Preparation for Induction

- Determine when, how and where you will start medication
- Advise patient not to use opioids for an appropriate amount of time prior to first dose
- Ensure that patient has arranged for transportation home from appointment for first dose
- Other contingency preparations?

Buprenorphine Induction

Patients dependent on short-acting opioids

Instruct patient to abstain from any opioid use for 12-24 hours (so they are in mild withdrawal at time of first buprenorphine dose)

If patient is not in opioid withdrawal at time of arrival in clinic, then assess time of last use and consider either having him/her return another day or wait until evidence of withdrawal seen

Buprenorphine Induction

Patients dependent on short-acting opioids (continued)

First dose: 2-4 mg sublingual buprenorphine

Monitor in clinic for 2+ hours after first dose

Can re-dose if needed (every 2-4 hours, if opioid withdrawal subsides then reappears)

Maximum first day dose of 8 mg

Buprenorphine Induction

Patients dependent on short-acting opioids (continued)

Begin with buprenorphine/naloxone combination tablets

If begin with buprenorphine monotherapy, switch to combination tablets as soon as possible, at same dose of buprenorphine (i.e., from 8 mg daily go to 8/2 mg daily)

Buprenorphine Induction

Patients dependent on long-acting opioids

Patient should have dose decreases until on ≤ 30 mg of methadone or the equivalent

Begin induction 24 hours after last dose of methadone,
48 hours after last dose of LAAM

Give no further methadone or LAAM once
buprenorphine induction is started

Buprenorphine Induction

Patients dependent on long-acting opioids (continued)

Use similar procedure as that described for short acting opioids, except more likely to use buprenorphine monotherapy for induction

Expect total first day dose of 8 mg sublingual buprenorphine

Buprenorphine Induction

Patients dependent on short- or long-acting opioids

On second day, have patient return to the office for assessment, second day dosing

Adjust dose accordingly based on patient's experiences on first day (i.e., higher dose if there were withdrawal symptoms after leaving your office; lower dose if patient was over-medicated at end of first day)

Buprenorphine Induction

Patients dependent on short- or long-acting opioids (continued)

Continue adjusting dose by 2-4 mg increments until an initial target dose of 12-16 mg is achieved for the second day

If continued dose increases are indicated after the second day, have the patient return for further dose induction (with a maximum daily dose of 32 mg)

Induction - The First Days

- Be prepared for frequent contact in early days
- Anxiety, fear and opioid use are common; strongly discourage opioid use - it confounds the clinical picture
- Advise patient not to increase the dose without consultation
- T/C - need for ancillary medication

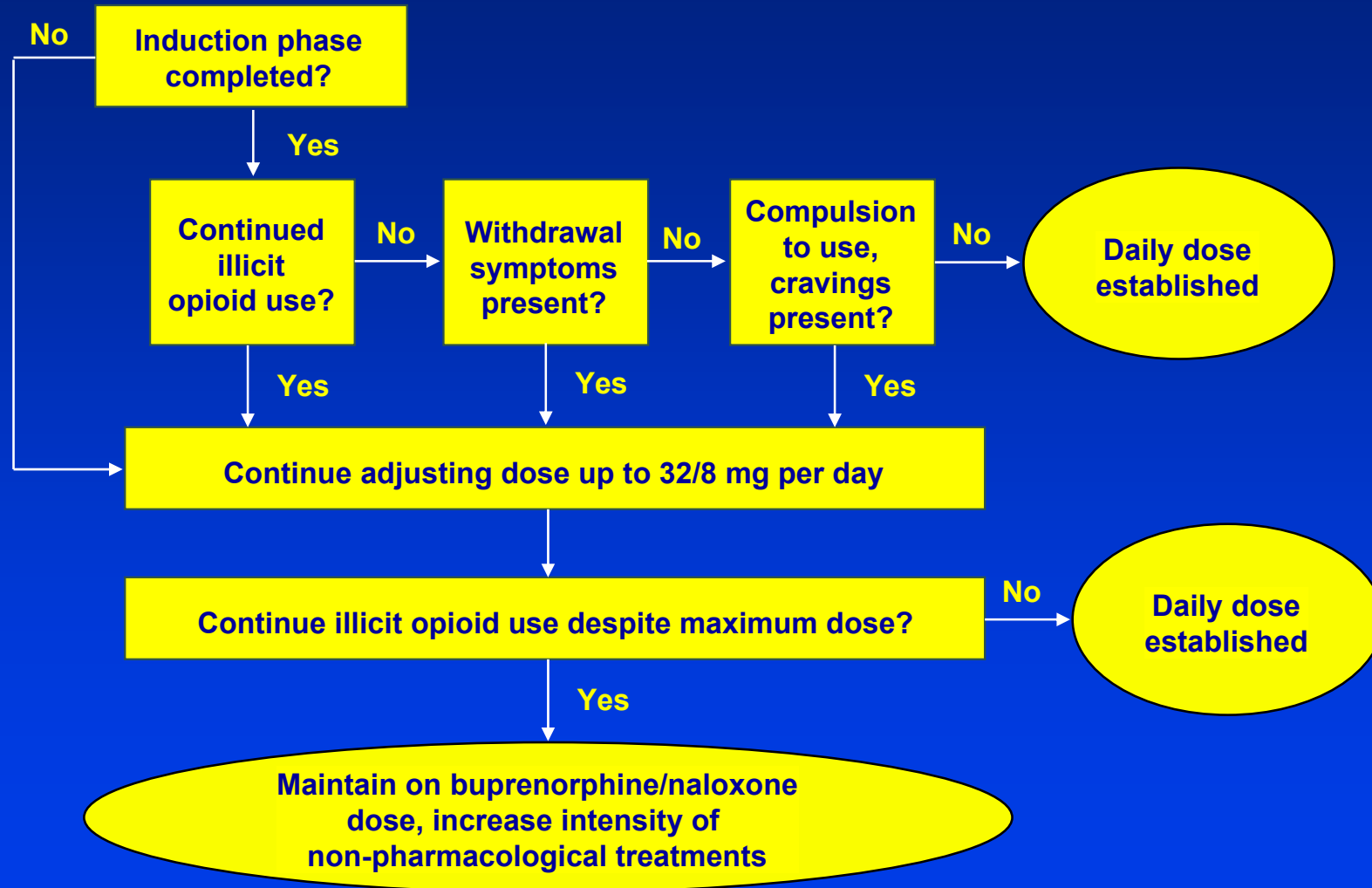
Buprenorphine Stabilization/maintenance

Stabilize on daily sublingual dose

Expect average daily dose will be somewhere between 8/2
and 32/8 mg of buprenorphine/naloxone

Higher daily doses more tolerable if taken sequentially
rather than all at once

Figure 7: Stabilization/maintenance



Buprenorphine/Naloxone Taper

- The ambivalent patient may want to discontinue
- Comprehensive treatment plan, patient desire, and acceptance
- Ideally issues related to opioid use are resolved
- Taper over weeks, months - maintain patient stability
- Psychosocial support
- Re-induce if relapse occurs

Withdrawal Using Buprenorphine

Withdrawal in ≤ 3 days (rapid)

Withdrawal over 4 to 30 days (moderate period)

Withdrawal over more than 30 days (long term)

Summary

Buprenorphine/Naloxone can be used in the office setting, as well as other therapeutic settings, for the treatment of opiate addiction. Physicians need to be qualified to prescribe buprenorphine/naloxone and need to arrange for appropriate ancillary services, including counseling for patients receiving buprenorphine/naloxone prescriptions.

Counselors need to understand the action and effects of buprenorphine in order to appropriately manage these patients (clients) and interact meaningfully with the prescribing physician.