Medication-Assisted Treatment (MAT) Management Of The Use Of Multiple Substances: Challenging Comorbidities And Conditions

Joe Sepulveda, M.D., ABPN, ABPM, FAPA, FASAM
Assistant Medical Director, Family Health Centers of San Diego
Medical Director, Substance Use Disorder Services
Medication-Assisted Treatment (MAT) Program
Psychiatric Nurse Practitioner Program
Voluntary Assistant Clinical Professor, UCSD Health Sciences—Dept. of Psychiatry
Diplomate of the American Board of Psychiatry and Neurology
Diplomate of the American Board of Preventive Medicine—Addiction Medicine
Fellow of the American Psychiatric Association
Fellow of the American Society of Addiction Medicine

Agenda

1. Current consensus for treating OUD

2. Management Of The Use Of Multiple Substances
   - Benzodiazepines
   - Methamphetamines

3. Challenging comorbidities and conditions
   - Pain conditions
   - Methadone—> Buprenorphine transition

Current consensus for treating OUD

Annals of Internal Medicine

SPECIAL ARTICLE

The Next Stage of Buprenorphine Care for Opioid Use Disorder

Stephen A. Martin, MD, EdM; Lisa M. Chiodo, PhD; Jordon D. Bosse, MS, RN; and Amanda Wilson, MD

Buprenorphine has been used internationally for the treatment of opioid use disorder (OUD) since the 1990s and has been available in the United States for more than a decade. Initial practice recommendations were intentionally conservative, were based on expert opinion, and were influenced by methadone regulations. Since 2003, the American crisis of OUD has dramatically worsened, and much related empirical research has been undertaken. The findings in several important areas conflict with initial clinical practice that is still prevalent. This article reviews research findings in the following 7 areas: location of buprenorphine induction, combining buprenorphine with a benzodiazepine, relapse during buprenorphine treatment, requirements for counseling, uses of drug testing, use of other substances during buprenorphine treatment, and duration of buprenorphine treatment. For each area, evidence for needed updates and modifications in practice is provided. These modifications will facilitate more successful, evidence-based treatment and care for patients with OUD.

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For author affiliations, see end of text.

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Current consensus for treating OUD

Table. Buprenorphine Care: Previous Approaches Compared With New Findings and Recommendations

Previous Approach	New Findings and Recommendations
A medical setting is needed for induction.	Home induction is also safe and effective (6).
Benzodiazepine and buprenorphine coprescription is toxic.	Buprenorphine should not be withheld from patients taking benzodiazepines (5).
Relapse indicates that the patient is unfit for buprenorphine-based treatment.	Relapse indicates the need for additional support and resources rather than cessation of buprenorphine treatment (43).
Counseling or participation in a 12-step program is mandatory.	Behavioral treatments and support are provided as desired by the patient (6).
Drug testing is a tool to discharge patients from buprenorphine treatment or compel more intensive settings.	Drug testing is a tool to better support recovery and address relapse (56).
Use of other substances is a sign of treatment failure and grounds for dismissal from buprenorphine treatment.	Buprenorphine treatment does not directly affect other substance use, and such use should be addressed in this context (43).
Buprenorphine is a short-term treatment, prescribed with tapered dosages or for weeks to months.	Buprenorphine is prescribed as long as it continues to benefit the patient (6)

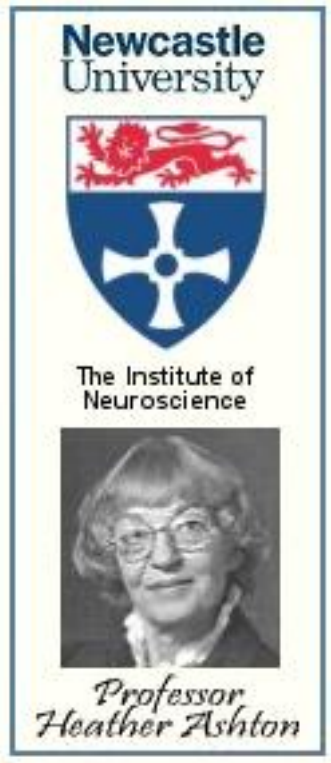
Management Of The Use Of Multiple Substances

Benzodiazepines

Many of the most commonly prescribed benzos are those which are most readily abused, including:	**ALPRAZOLAM** (Xanax) 	**CLONAZEPAM** (Klonopin) 	**CHLORDIAZEPOXIDE** (Librium) 
DIAZEPAM (Valium) 	**LORAZEPAM** (Ativan) 	**TEMAZEPAM** (Restoril) 	**TRIAZOLAM** (Halcion) 

Benzodiazepines

- Do not stop MAT for OUD (FDA 2017)
- Individualized taper has best evidence
  - Ashton Method (https://benzo.org.uk/manual/)
  - Canadian Deprescribing Guidelines (https://www.deprescribingnetwork.ca/)
  - VA National Center for PTSD Benzo Taper Recommendations (See references section)



Canadian Deprescribing Network

VA U.S. Department of Veterans Affairs

Benzodiazepines—Know your Immunoassay

- Standard assays detect
  - Nordiazepam & Oxazepam
- Immunoassays may not detect
  - Clonazepam
  - Alprazolam
    - Lorazepam
    - Temazepam

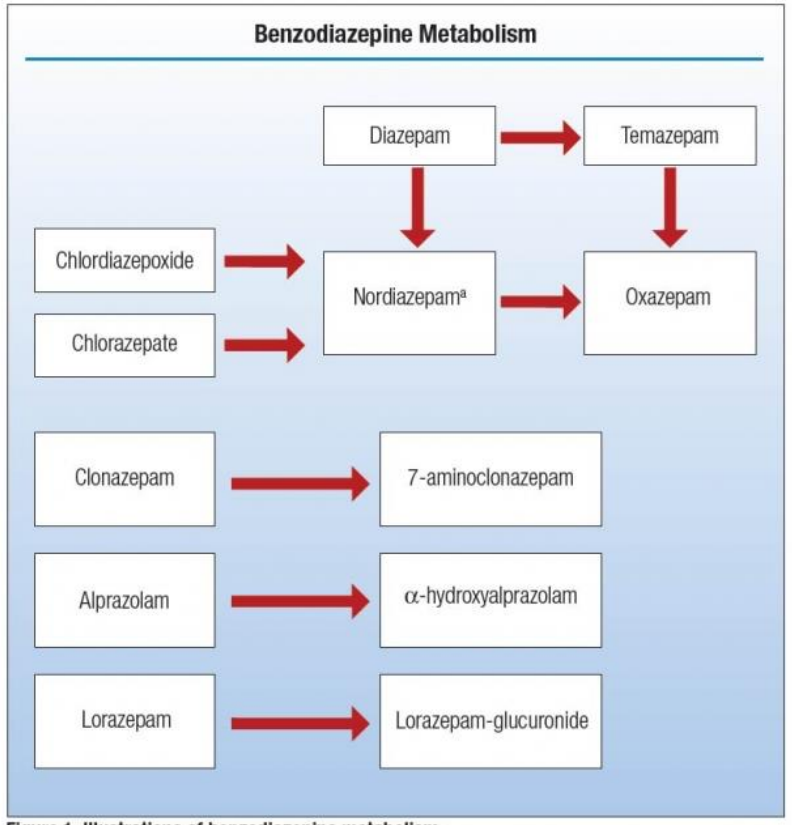
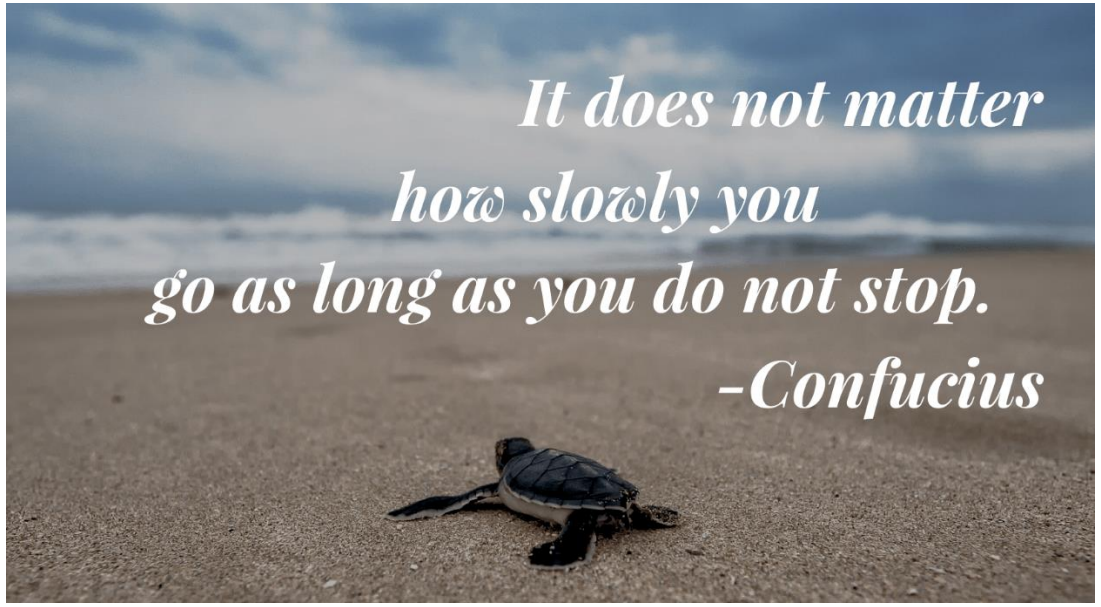


Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
[a]Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam

Benzodiazepines

- Pharmacologic Tapering Strategies
  - Gradual Taper of same Benzo taken by patient
  - Substitution of long-acting Benzo
    - *Exception:* Older patients already on short-acting, taper this first
  - Set clear goals with patients
  - Frequent follow up visits
  - Chronic users = slow taper over **MONTHS**
  - Scheduled, not PRN dosing



THM: No clear evidence-based guidelines on taper rates

Benzodiazepines

- Potency Equivalents

Benzodiazepines[5]	Half-life (hrs)[1] [active metabolite]	Approximately Equivalent Oral dosages (mg)[3]
Alprazolam (Xanax)	6-12	0.5
Bromazepam (Lexotan, Lexomil)	10-20	5-6
Chlordiazepoxide (Librium)	5-30 [36-200]	25
Clobazam (Frisium)	12-60	20
Clonazepam (Klonopin, Rivotril)	18-50	0.5
Clorazepate (Tranxene)	[36-200]	15
Diazepam (Valium)	20-100 [36-200]	10
Estazolam (ProSom)	10-24	1-2
Flunitrazepam (Rohypnol)	18-26 [36-200]	1
Flurazepam (Dalmane)	[40-250]	15-30
Halazepam (Paxipam)	[30-100]	20
Ketazolam (Anxon)	30-100 [36-200]	15-30
Loprazolam (Dormonoct)	6-12	1-2
Lorazepam (Ativan)	10-20	1
Lormetazepam (Noctamid)	10-12	1-2
Medazepam (Nobrium)	36-200	10
Nitrazepam (Mogadon)	15-38	10
Nordazepam (Nordaz, Calmday)	36-200	10
Oxazepam (Serax, Serenid, Serepax)	4-15	20
Prazepam (Centrax)	[36-200]	10-20
Quazepam (Doral)	25-100	20
Temazepam (Restoril, Normison, Euhypnos)	8-22	20
Triazolam (Halcion)	2	0.5

Benzodiazepines

- Benzo Withdrawal
  - May occur after ≥4 weeks of benzo use
  - Occurs within 1-7 days of DC use
  - Can last 4-14 days (short vs. long half-life, respectively)

- Physical symptoms
  - Stiffness, weakness, GI disturbance, flu like symptoms, paresthesia, visual disturbances, seizures
- Psychological symptoms
  - Anxiety/irritability, Insomnia/nightmares, depersonalization, decrease memory and concentration, delusion and hallucinations, depression

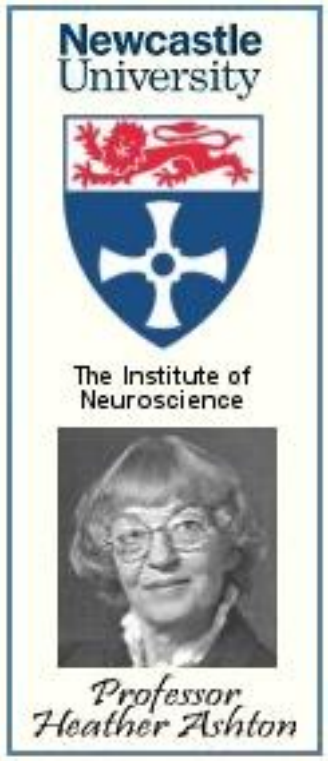
THM: Slow the taper if needed

Benzodiazepines

- Tapering Strategy #1 for Xanax
  - Taper by lowest commonly prescribed dose
    - E.g. Xanax 0.25 mg
  - Taper every 1-2 weeks (longer preferred)
  - If withdrawal occurs
    - Hold dose then resume or switch to a longer-acting benzodiazepine and resume.
      - E.g. Clonazepam or Diazepam
- If switch to long-acting, taper by the lowest commonly prescribed dose.
  - E.g. Clonazepam taper by 0.5 mg
  - E.g. Diazepam taper by 5mg
- **Key**—> Clonazepam 0.5mg is equivalent to ~ 10 mg of Diazepam. If withdrawal occurs…
  - Transition to Diazepam 5mg bid.
    - Continue taper
      - E.g. Diazepam 2 mg qam + 5mg qhs.

Benzodiazepines

- Taper Strategy #2 (Ashton Manuel)



Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	--	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	--	diazepam 20mg	40mg

Benzodiazepines

- Tapering Strategy #3 (VA rec's)

Milestone Suggestions		Example: Lorazepam 4 mg bid Convert to 40 mg diazepam daily
Week 1		35 mg/day
Week 2	Decrease dose by 25%	30 mg/day (25%)
Week 3		25 mg/day
Week 4	Decrease dose by 25%	20 mg/day (50%)
Week 5-8	Hold dose 1-2 months	Continue at 20 mg/day for 1 month
Week 9-10		15 mg/day
Week 11-12	Decrease dose by 25% at week 11	10 mg/day
Week 13-14	Decrease dose by 25% at week 13	5 mg/day
Week 15		discontinue

Fuller MA, Sajatovic M. (2009). Drug Information Handbook for Psychiatry. 7th ed. Hudson, OH: Lexi-Comp Inc.

Perry PJ, et al. (1997) Psychotropic Drug Handbook, 8th ed. Baltimore, MD: Lippincott Williams & Wilkins.

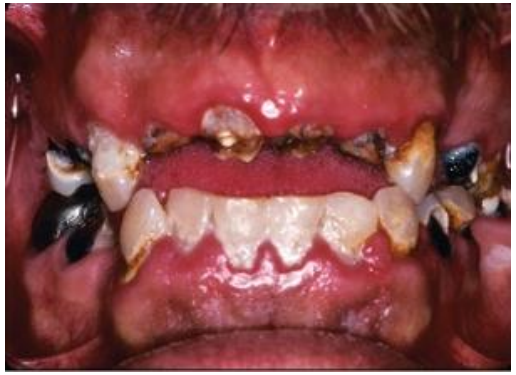
Benzodiazepines

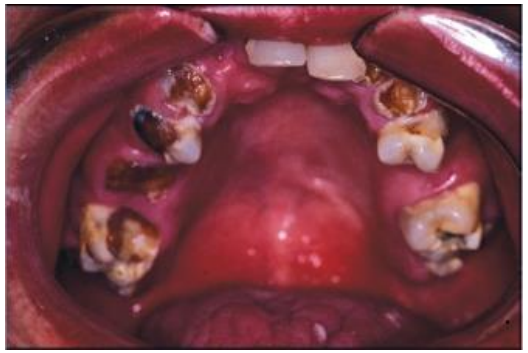
1. Augmentation
    - Valproate
    - Gabapentin
    - Pregabalin
    - Topiramate
        - Carbamazepine
        - Oxcarbamzepine
2. Support Medications—No evidence supporting one over the other… trial and error.
    - Antihistamines
        - Hydroxyzine
    - Adrenergic Antagonist
        - Clonodine, Propranolol
    - Muscle relaxants
        - Baclofen, Tizanidine
    - Sedating Antidepressants
        - Trazodone, Mirtazapine

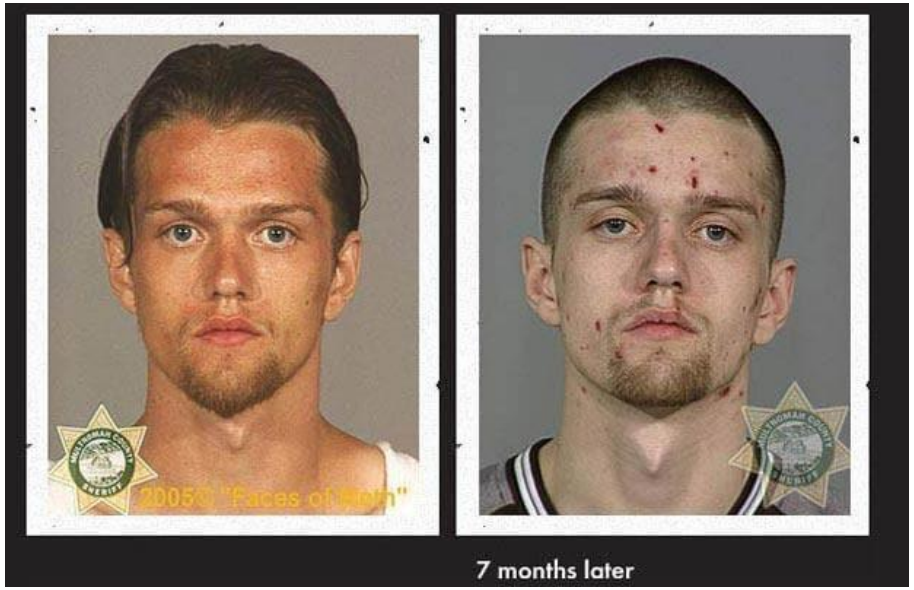
Methamphetamines

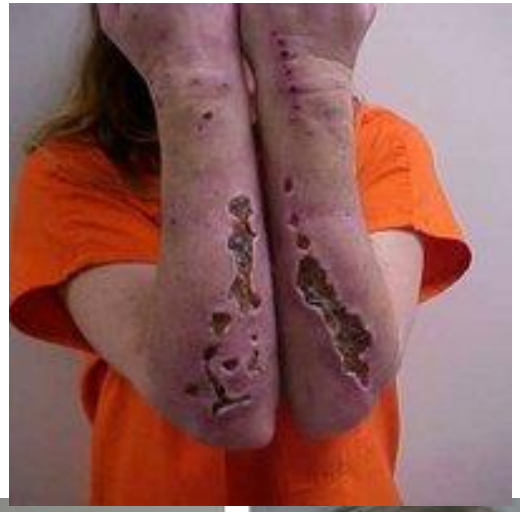
Methamphetamines

Methamphetamines









Methamphetamines

- Immunoassay Drug Screen
  - Detection window ~2-3 days
  - False positives: Pseudoephedrine, labetolol, ranitidine, trazodone, TCA's... etc.
  - 2 methamphetamine isomers: D (CNS) and L (Peripheral)

Methamphetamines

- Basic Assumptions
  - Substance use can be reduced using operant conditioning
  - Useful in promoting treatment retention and adherence
  - Incentives for negative urine test useful in decreasing drug use

Methamphetamines

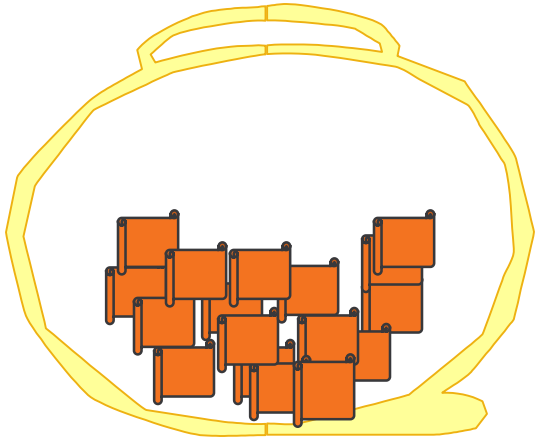
- Key Concepts
  - Behavior to be modified (e.g. stimulant use) must be objectively measured
  - Behavior to be modified (e.g. UDS) must be monitored frequently
  - Reinforcement must be immediate
  - Penalties for unsuccessful behavior (e.g. +UDS) include reduced voucher amount

Nancy Petry's Fishbowl

Fishbowl Method

Incentive = draws from a bowl

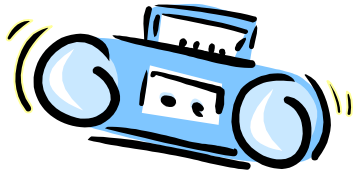
- Draws earned for each negative urine
- Number of draws can escalate
- Bonus draws can be given for consecutive weeks of abstinence



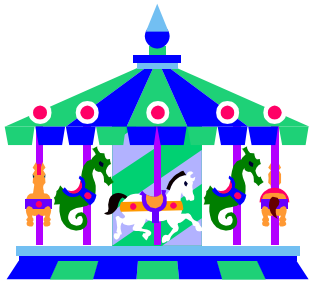
Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt

Half the slips are winners
Win frequency inversely related to cost

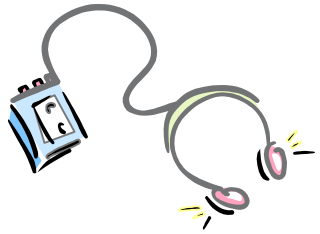
- largest chance of winning a small $1 prize

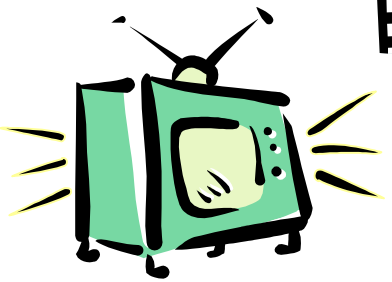


- moderate chance of winning a large $20 prize



- small chance of winning a jumbo $100 prize





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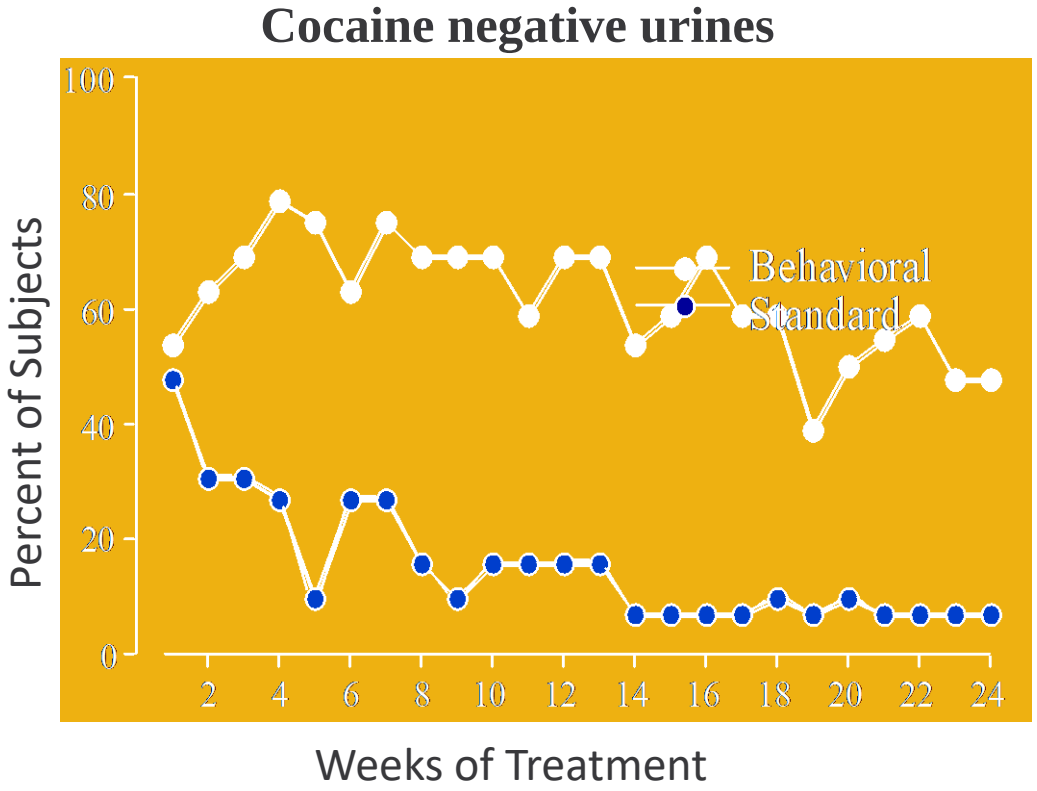
Voucher Incentives in Outpatient Treatment

Higgins et al. Am. J. Psychiatry, 1993



Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt

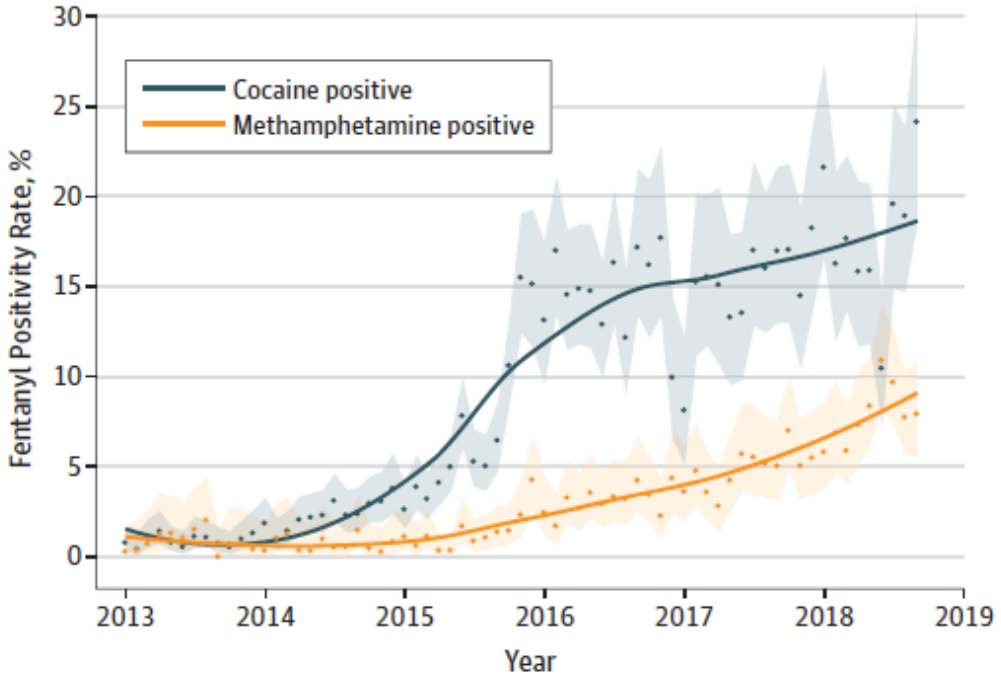
Methamphetamines

1. MATRIX model
   - Research-based framework for engaging stimulant abusers in treatment and helping achieve abstinence

2. Composed of
   - Group psychotherapy
   - Individual counseling
   - Family therapy
   - Contingency management
   - Crystal meth anonymous (self-help groups)
   - Treatment of co-occurring disorders

Methamphetamines—Fentanyl

Figure. Nonprescribed Fentanyl Positivity Among Urine Drug Test Results Positive for Cocaine or Methamphetamine



Dots represent monthly fentanyl positivity values; shaded areas, binomial 95% CIs.

Methamphetamines—Mirtazapine 30mg qhs

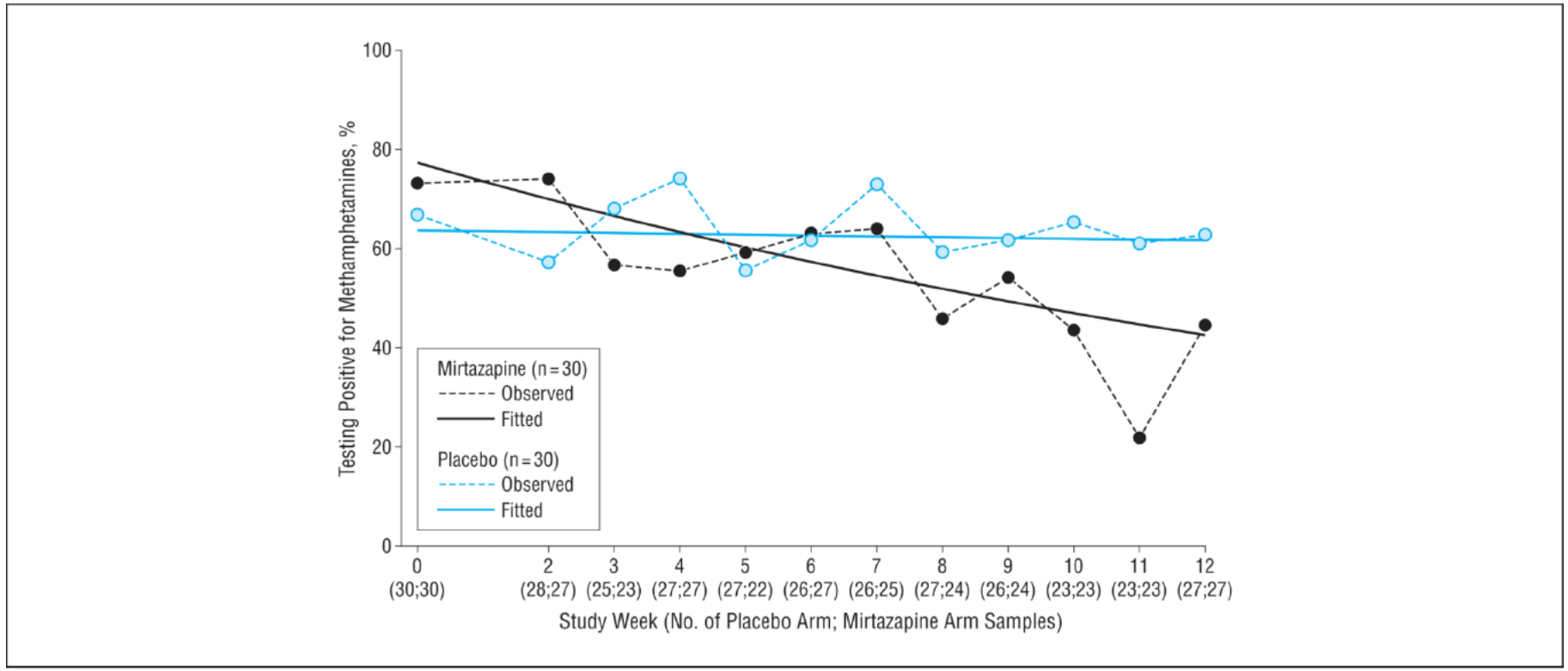


Figure 2.
Observed and fitted weekly urinalysis results, according to treatment arm. Fitted trend lines are based on the primary outcome model.

Methamphetamines—Bupropion

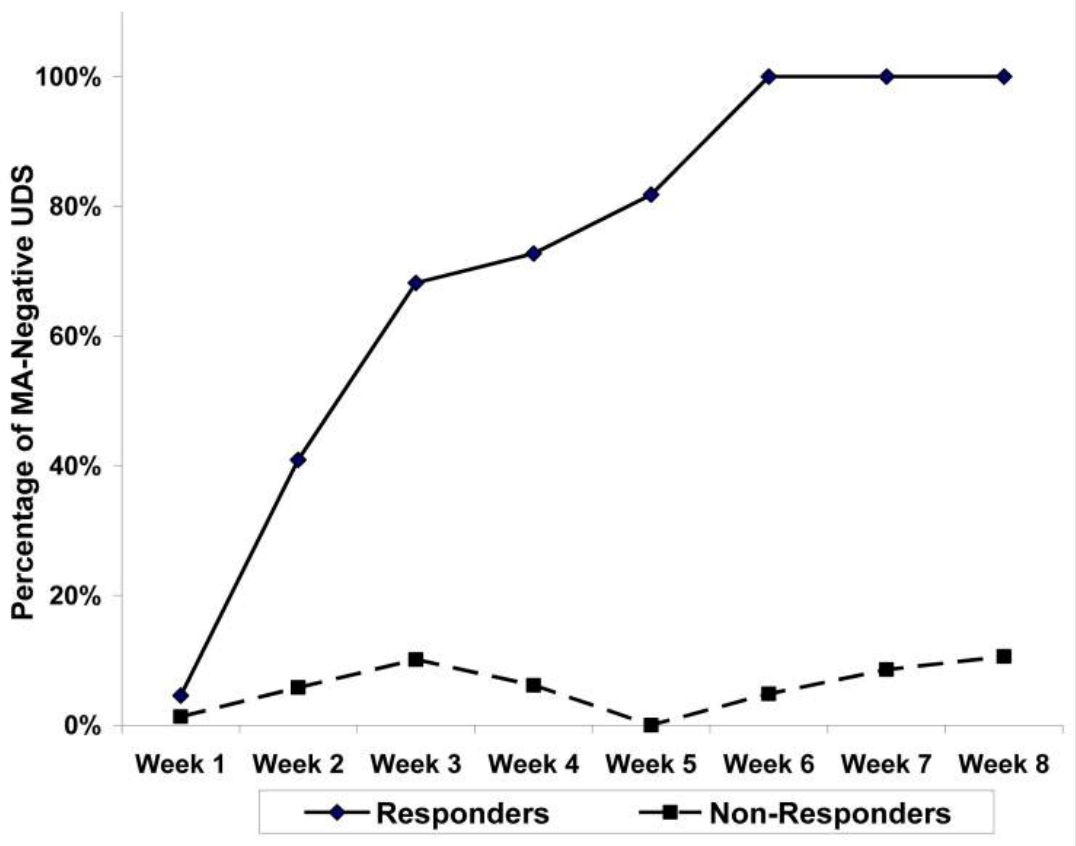
Randomized trial of bupropion SR 150 mg bid vs placebo for 12 weeks in methamphetamine users with ***less than daily meth use***

Total sample	Bupropion (N=41)	Placebo (N=43)	P value
End of treatment abstinence	29% (12)	14% (6)	0.087

Only 32% (13/41) of bupropion participants were deemed medication adherent via week 6 plasma bupropion level. Adherence was strongly associated with end of treatment meth abstinence.

Bupropion only	Adherent (N=13)	Non-adherent (N=28)	P value
End of treatment abstinence	54% (7)	18% (5)	0.018

Methamphetamines—Naltrexone LAI + Bupropion XL



- Naltrexone 380 mg monthly + Bupropion XL 300 mg – 450 mg daily.
- Warrants further study

Methamphetamines—Lower strength evidence

Topiramate

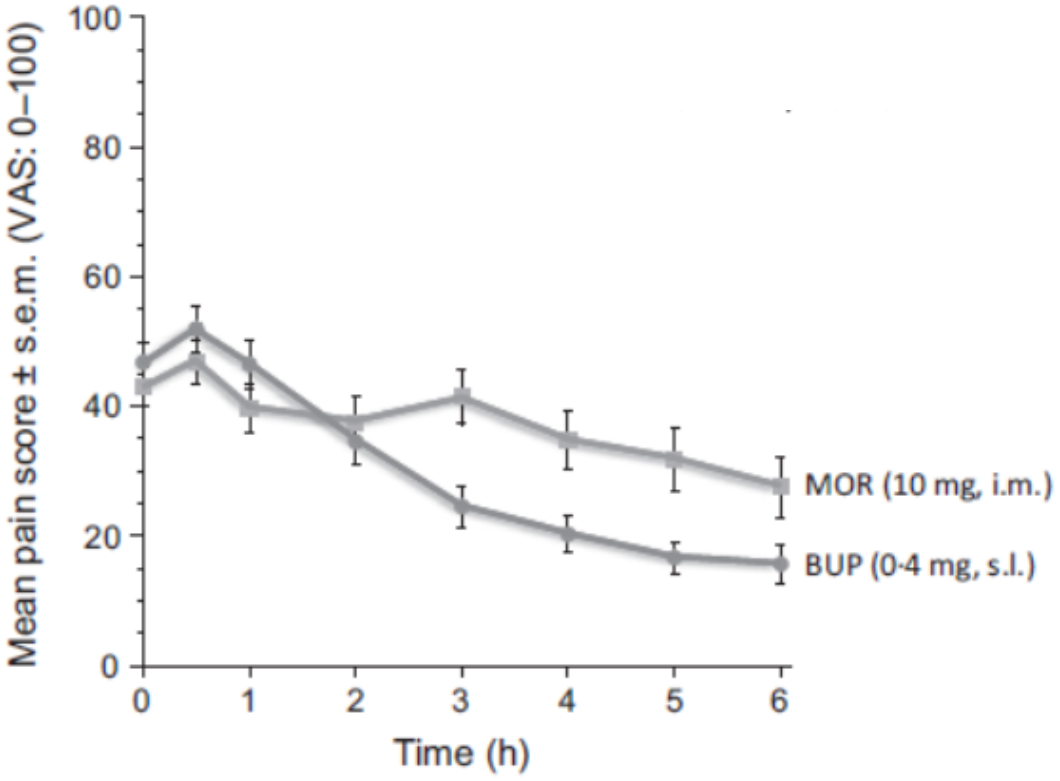
- May be more effective if UDS negative at baseline
- Target maintenance dose 200mg/day

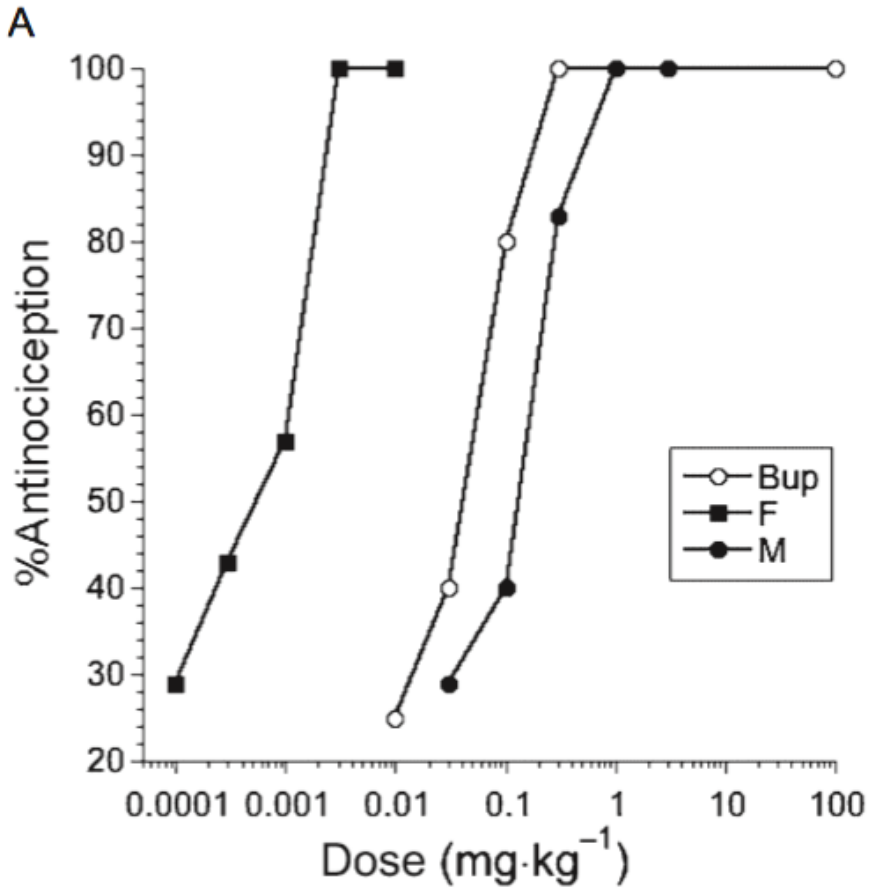
THM: Does not appear to promote abstinence in MA users but can reduce the amount taken and reduce relapse in those who are already abstinent

Challenging comorbidities and conditions

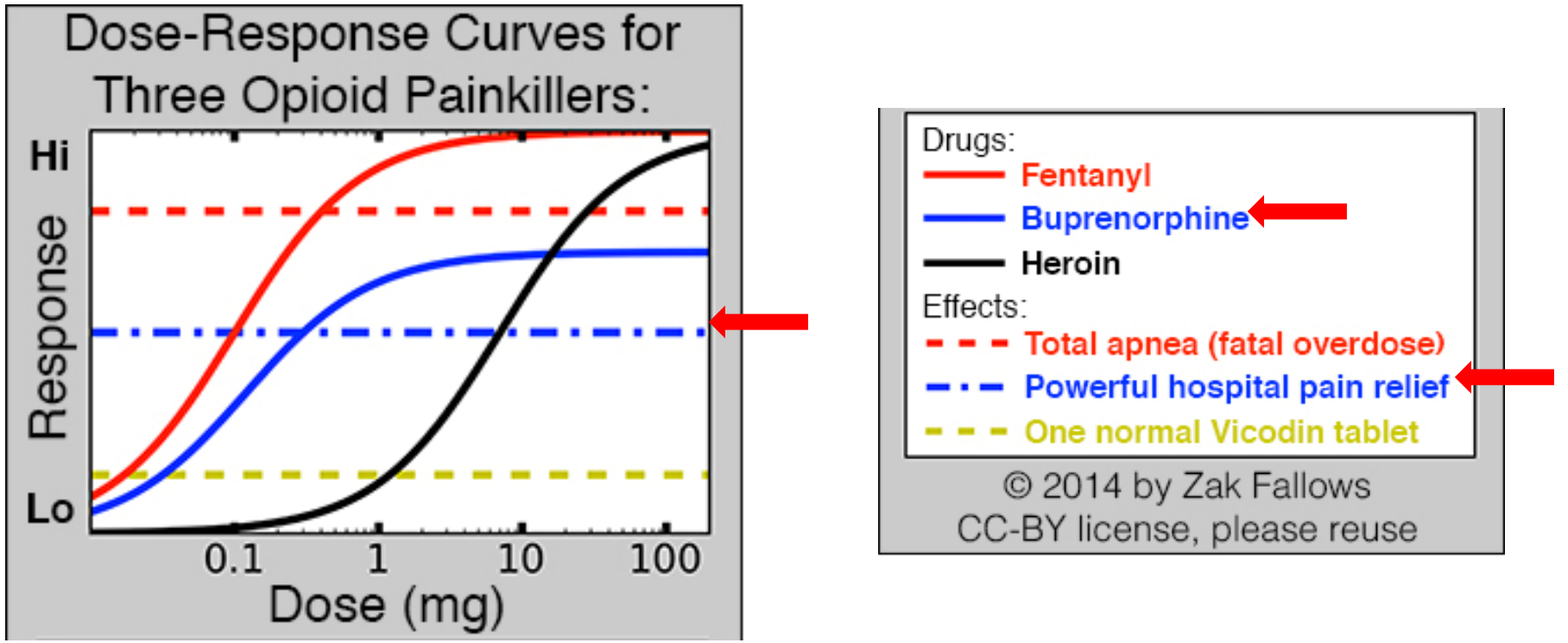
Pain Conditions

Pain Conditions—Buprenorphine

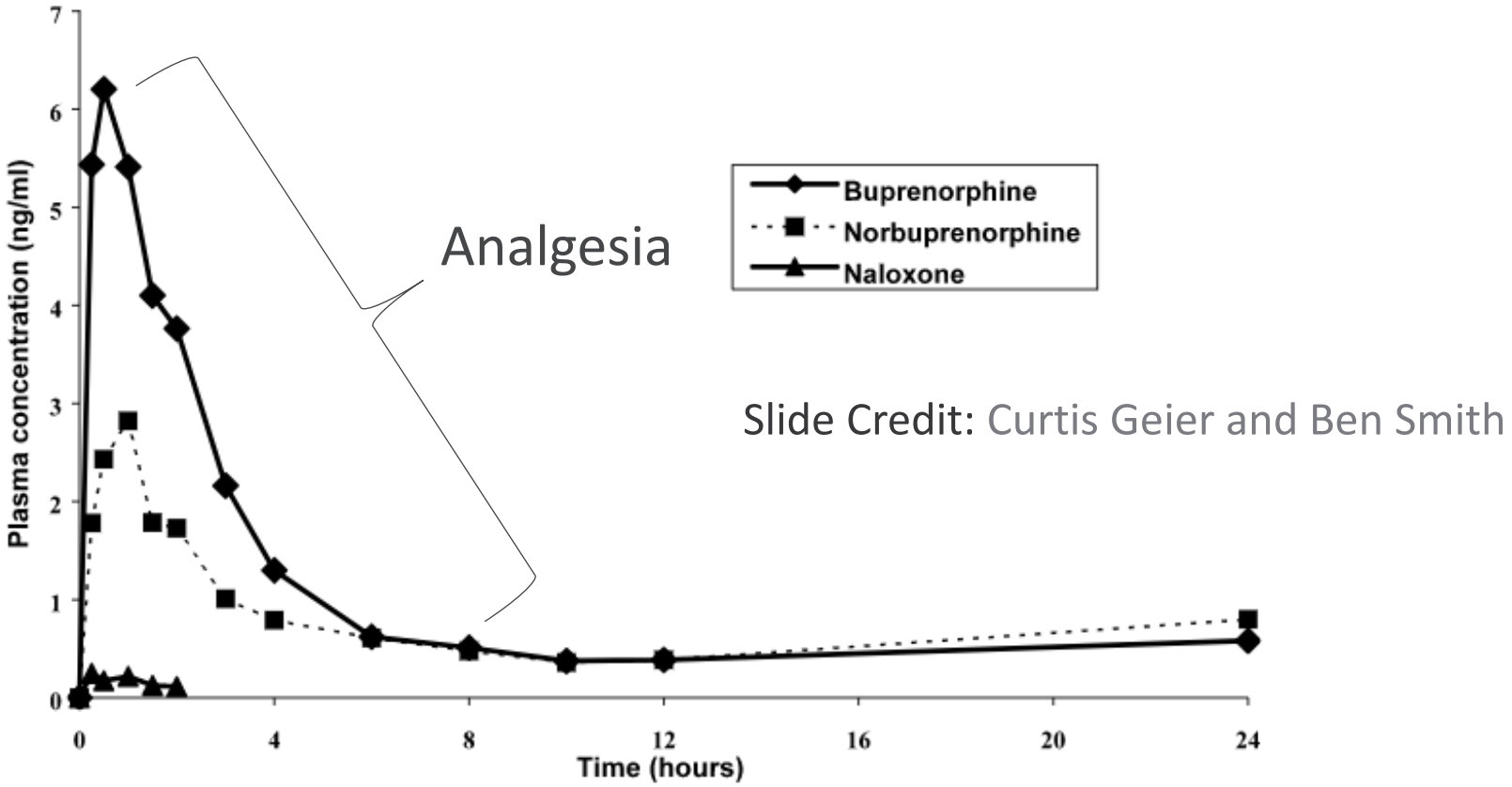




Pain Conditions—Buprenorphine



Buprenorphine Pharmacokinetics



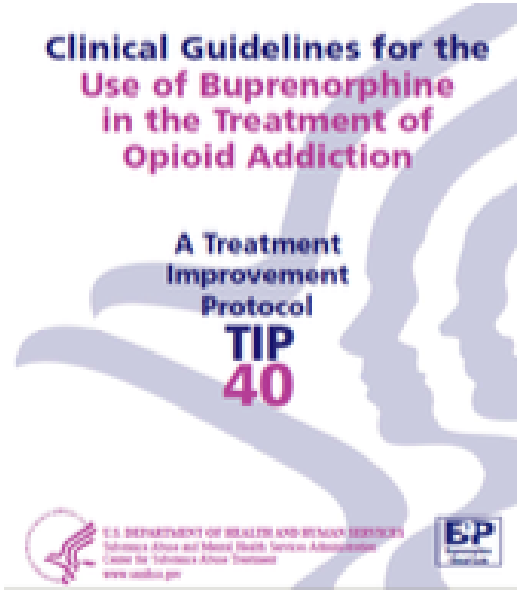
Slide Credit: Curtis Geier and Ben Smith

Fig. 4. The time course of plasma levels of buprenorphine, norbuprenorphine and naloxone for a subject receiving a sublingual dose of the combination tablet of buprenorphine (16 mg) and naloxone (4 mg) (data from Jones et al., 1997).

Pain Conditions—Buprenorphine & Surgery

Pain Conditions—The Old Recommendations

"While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids."



Pain Conditions

	All Buprenorphine	Buprenorphine Given	Buprenorphine NOT given
1st 24 hour MSE	200 +/-128.6	155.2 +/-135.5	245.5 +/- 109.3
NSAID	31.8	18.2	45.5
Ketamine	63.6	27.3	100
Days APS	4.5 +/-3.3	3.0 +/-1.7	5.9 +/-3.9

Chart adopted from Andrea Rubinstein, MD - CSAM Webinar 6: managing Acute and Perioperative Pain in Patients on Medication-Assisted Treatment (MAT).

Pain Conditions

1. Buprenorphine Sublingual
    - Analgesia duration ranges from 6-8 hours
        - Analgesia will likely require multiple daily dosing–TID or QID
        - OUD cravings controlled on Once Daily or BID dosing
    - Peak plasma concentration SL ~90 mins
    - Brain levels exceed plasma levels as Bup is very lipophilic
2. Transdermal Buprenorphine patch
    - Duration ~7 days
    - 5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
3. Buprenorphine Buccal Film
    - Greater bioavailable dose than SL tablets or film
    - BID dosing
    - 300 mcg bup buccal film dose is equivalent to 20 mcg transdermal bup patch

Pain Conditions

Table 6 Oral morphine to transdermal buprenorphine equivalents[a]

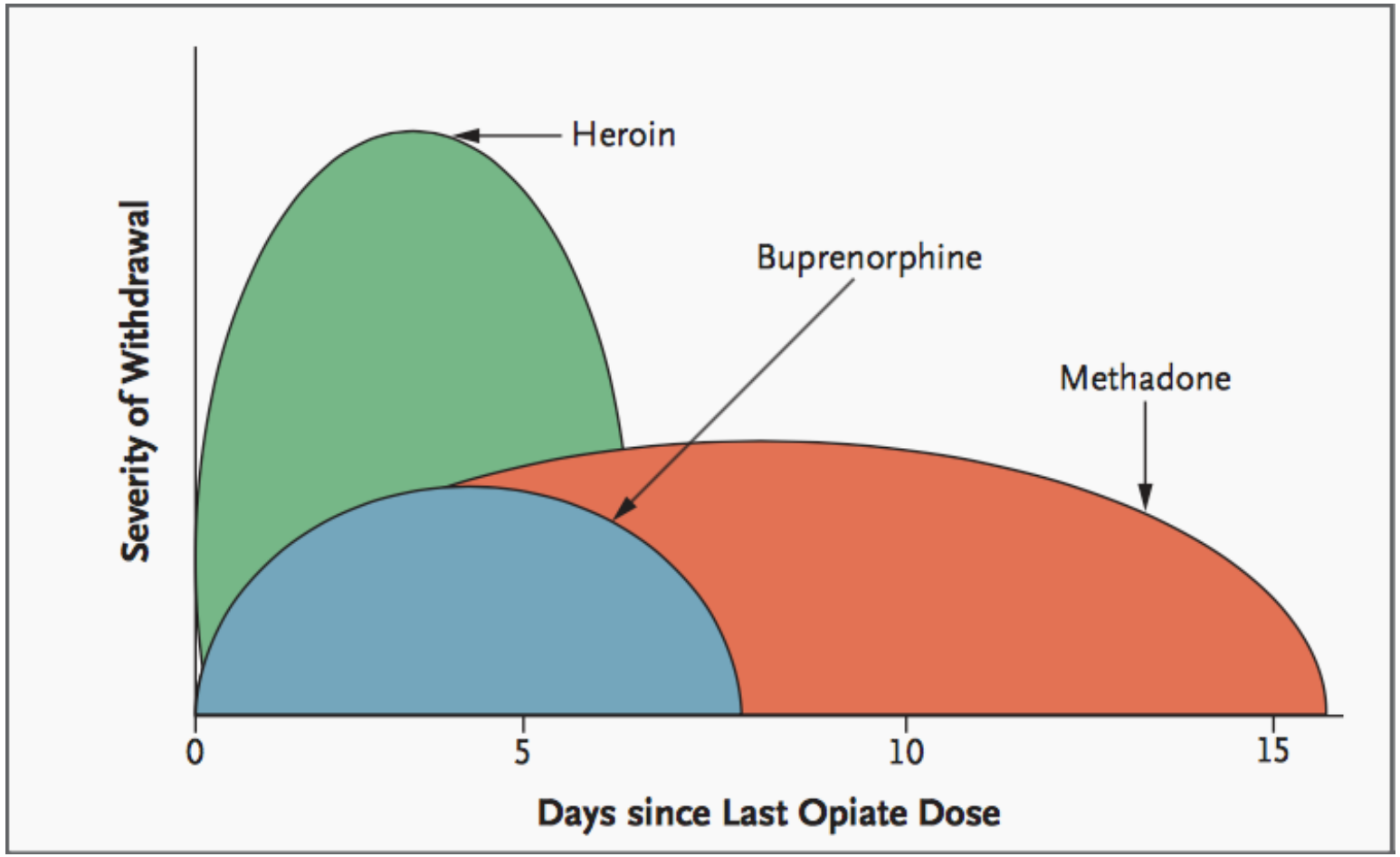
Oral morphine (mg/day)	Transdermal buprenorphine (μg/h)
12	5
24	10
48	20
84	35
126	52.5
168	70

[a]From the palliativedrugs.com newsletter, November/December 2006

Methadone


500ml
Methadone
Hydrochloride
DTF 1mg/1ml
Oral Solution
central nervous system

Methadone


Heroin
Buprenorphine
Methadone
Severity of Withdrawal
0
5
10
15
Days since Last Opiate Dose

Methadone

1. Switching to Suboxone…
   - Elimination ½ life at steady state ~28 hrs
     - LONG-ACTING
   - Outpatient induction
     - Recommend patient taper to 30-40 mg per day for one week.
     - After 1 week DC Methadone for 48-72 hrs.
       - **Key→ until develop mild-moderate withdrawal sx's.**
     - Consider beginning induction with Buprenorphine mono-product for 1-2 days.
       - Dose 2 mg at a time
     - Transition to Buprenorphine/Naloxone combination product

THM: Recommend office-based induction when you first begin doing this.

THM: Recommend prescribing comfort medication for the induction

Methadone

1. Comfort Medication
    - Withdrawal support
        - Clonidine 0.1 mg q6 hr prn
        - Phenergan 25mg q4-6 hr prn
        - Zofran 8 mg q8-12 hr prn
        - Loperamide 2 mg prn
    - Pain Support
        - Acetaminophen 325 mg q4-6 hr prn muscle/joint pain
        - Ibuprofen 600 mg q6-8 hr prn muscle/joint pain
        - Cyclobenzaprine 10 mg q8 hr prn muscle cramps
    - Insomnia Support
        - Hydroxyzine 25 mg, 1-2, qhs prn

References

1. https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/23_Benzodiazepine_Provider_AD_Quick_Reference_Guide_IB10_929.pdf
2. Colfax, GN, et al., Arch Gen Psychiatry. 2011 Nov.; 68(11): 1168-1175
3. Heinzerling KG., Addiction. 2014 Nov.; 109(11): 1878-1886
4. Mooney LJ, et al., J Addict Med. 2016 Jul-Aug;10(4):236-43.
5. Elkashef A, et al., Addiction. 2012 Jul; 107(7): 1297–1306.
6. Chan B., et al., Addiction. 2019 Jul 22. doi: 10.1111/add.14755.
7. CBHSQ 2018 NSDUH 2017
8. Willenburg ML. Am Fam Physician 2009.
9. Raffa RB, Haidery M, et al. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther. 2014 Dec;39(6):577-83.
10. Ding Z, Raffa RB, Identification of an additional supraspinal comonent to the analgesic mechanism of action of buprenorphine. Br J Pharmacol. 2009 Jul; 157(5):831-43.
11. https://ocw.mit.edu/courses/experimental-study-group/es-s10-drugs-and-the-brain-spring-2013/
12. Macintyre PE, Russel RA, et al., Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care. 2013 Mar, 41(2):222-30.
13. Davis, MP, et al., "Treating Chronic Pan: An overview of clinical studies centered on buprenorphine option. Drugs. 2018 Aug;78(12):1211-1228.
14. Kosten TR, O'Connor PG., Management of drug and alcohol withdrawal. NEJM. 2003 May 1;348(18):1786-95.
15. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014 Jul 1;71(7):821–6.
16. Chiang CN, et al., Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug Alcohol Depend. 2003 May 21;70(2 Suppl):S39-47.


ANY
QUESTIONS
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