

## Implementing Buprenorphine Treatment in Opioid Treatment Programs

Webinar 2, October 3, 2018

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Webinar 1: operational and logistical steps, 9/27/2018



## Background for these webinars

- The Drug Medi-Cal/Organized Delivery System requires addition of sublingual buprenorphine to the opioid agonist treatment medications offered in Opioid Treatment Programs (known in CA statute as Narcotic Treatment Programs, or NTPs)  
<https://www.dhcs.ca.gov/provgovpart/Pages/Drug-Medi-Cal-Organized-Delivery-System.aspx>, IN 16-048
- The first webinar covered the logistics of including buprenorphine as part of regular care in the clinic.
- This webinar is focused on clinical pharmacology, patient selection and flow of medical care.
- Some parts of clinic logistics are a team effort, such as choosing medication, and timing of induction, so overlap in both webinars

## Educational Objectives

- ▶ Participants will:
  - ▶ Discuss both medications at intake as part of informed consent to treatment.
  - ▶ Consider safety, effectiveness and patient preferences in choice of medication
  - ▶ Set up intake process to avoid precipitated withdrawal, while maintaining treatment on demand.
  - ▶ Participate in changes in operations manual
    - ▶ Patient selection criteria
    - ▶ Patient orientation materials
    - ▶ Procedures for observed dosing
    - ▶ Circumstances for transfer to primary care

## Medication selection, comparisons related to patient flow

Methadone	Buprenorphine
Oral liquid, easy to observe dosing	Sublingual tablet or film, what is observed dosing?
One preparation, continuum of dose	Various discrete doses, in various forms, some with naloxone
Only available for opioid use disorder treatment in OTPs or OTP satellite settings	Available as office based prescription, raises option of transfer of stable patients to primary care
Overdose is a danger, in particular during first week of treatment	Better safety profile for respiratory depression, may even be protective of overdose
Intake: same day dose commonly done	May have to schedule first dose to avoid precipitated withdrawal

## Buprenorphine, review of clinical pharmacology

- Some basic slides used over the last 15+ years in physician trainings.

## Types of opioids, glossary



"flower of joy"



The sap is extracted by slitting the pod

Types of opioids	Source	Examples
Natural opiates	From the poppy	Morphine, Thebaine, Codeine, Opium
Semi-synthetic	from the poppy, but processed further	Heroin, Oxycodone
Synthetic	Designed in the lab, effect similar to natural	Methadone, Fentanyl, Etc.

Endogenous opioids:  
three main families  
opioid receptors: three  
main receptors

- (Mu receptor most clinically significant in addiction medicine)

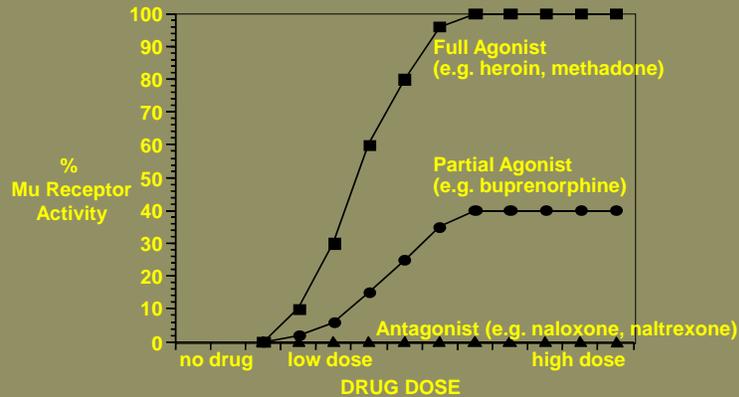
Opioid receptor	Mu receptor	Kappa receptor	Delta receptor
Endogenous opioid	Beta endorphins, enkephalin	Dynorphins	Beta endorphins, enkephalin
Effects	<b>Euphoria, analgesia, resp. depression, miosis</b>	Analgesia, dysphoria, psychosis	?

See chapter 9, [ASAM Principles of Addiction Medicine](#), page 135

## Receptor affinity

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Naloxone, naltrexone or buprenorphine show very strong affinity and will displace full agonists like heroin and methadone
  - Note receptor binding strength (strong or weak), is NOT the same as receptor activation (agonist or antagonist)
  - This is clinically important in overdose rescue (naloxone), and in timing of first dose (buprenorphine, naltrexone).
  - If receptor activation is less, a drug with strong affinity can precipitate painful withdrawal.

## COMPARISON OF MU RECEPTOR ACTIVATION LEVELS, RESPIRATORY DEPRESSION



## OPIOID PHARMACOTHERAPY FOR OUD (AND OVERDOSE RESCUE)

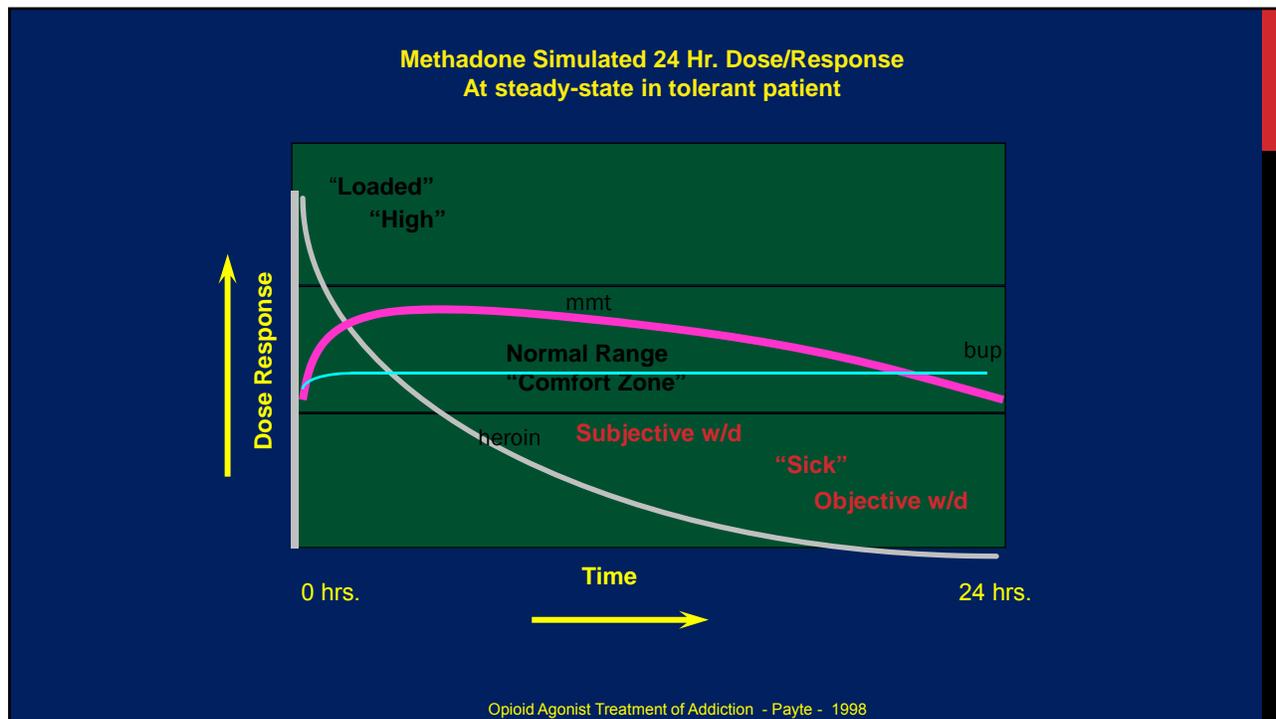
Most evidence and 'gold standard' is agonist maintenance, using methadone or buprenorphine. (Many studies comparing bup/methadone in past five years.)

Medically supervised withdrawal should lead to ongoing care, and include easy transfer to agonist maintenance if relapse is imminent.

Antagonist treatment is available, less track record. May be best considered in cases where a significant period of abstinence has been achieved (hospitalization, incarceration, residential treatment)

Rescue naloxone co-prescribing and furnishing is legal in California, and strongly advocated.

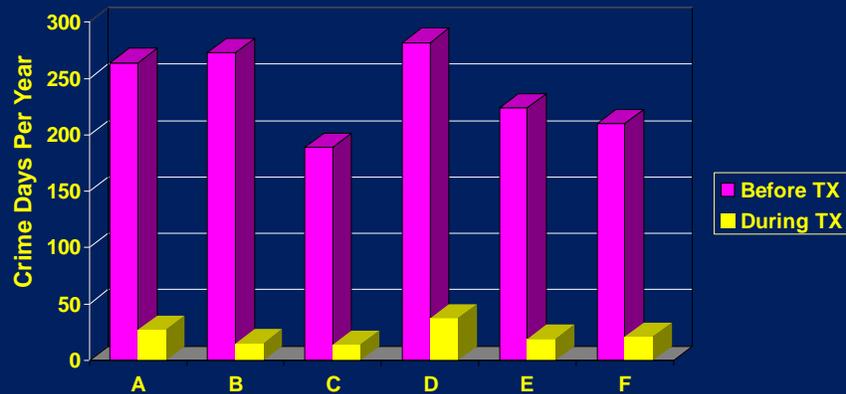
Standard pharmacotherapy includes psychosocial treatment. Some evidence that 'minimal' treatment (medication alone) works, too.



Many outcomes of methadone treatment are also seen in buprenorphine maintenance

- Reduction of drug use
- Excellent retention – although slightly lower than methadone
- Reduction in HIV and Hepatitis C seroconversion
- Control of withdrawal signs and symptoms

## CRIME AMONG 491 PATIENTS BEFORE AND DURING MMT AT 6 PROGRAMS



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

Opioid Agonist Treatment of Addiction - Payte - 1998

## CRIMINAL CHARGES AND OFFICE-BASED BUPRENORPHINE:

. Rastegar et al: [Subst Use Misuse](#). 2016 Jun 6;51(7):803-11

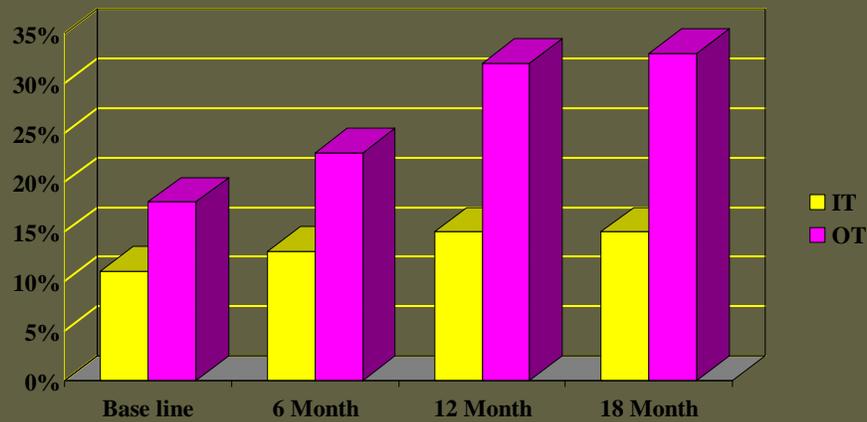
*“Criminal Charges Prior to and After Enrollment in Opioid Agonist Treatment: A Comparison of Methadone Maintenance and Office-based Buprenorphine.”*

Records review of 500 patients, half on each treatment medication.

Criminal records in two years prior and two years after enrollment showed that methadone enrollment was associated with reduction in criminal charges, but buprenorphine was not.

(Buprenorphine was office-based, ie venue was not controlled)

## HIV CONVERSION IN TREATMENT



HIV infection rates by baseline treatment status. In treatment (IT) n=138, not in treatment (OT) n=88

Source: Metzger, D. et. al. J of AIDS 6:1993. p.1052

Opioid Maintenance Pharmacotherapy - A Course for Clinicians - 1997

## MAINTENANCE MAT ALSO ASSOCIATED WITH REDUCED HCV INCIDENCE

*Nolan, et al: Addiction, 2014:*

HCV testing every six months of high risk cohort in Vancouver: HCV infection protection by MMT enrollment, duration and dose.

*Tsui, et al: JAMA Intern Med, 2014:*

Young adult injectors who reported methadone or buprenorphine maintenance had lower HCV incidence. (UFO study)

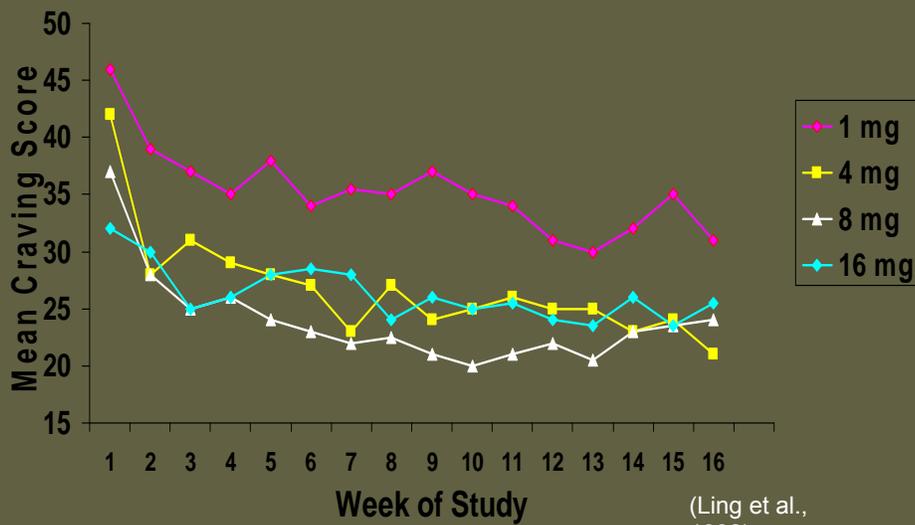
## MAT SUPPORTS HIV AND HCV TREATMENT

Methodone and buprenorphine MAT improve viral suppression and medication adherence in HIV and also for HCV treatment.

*Springer, PloS ONE, May 2012*

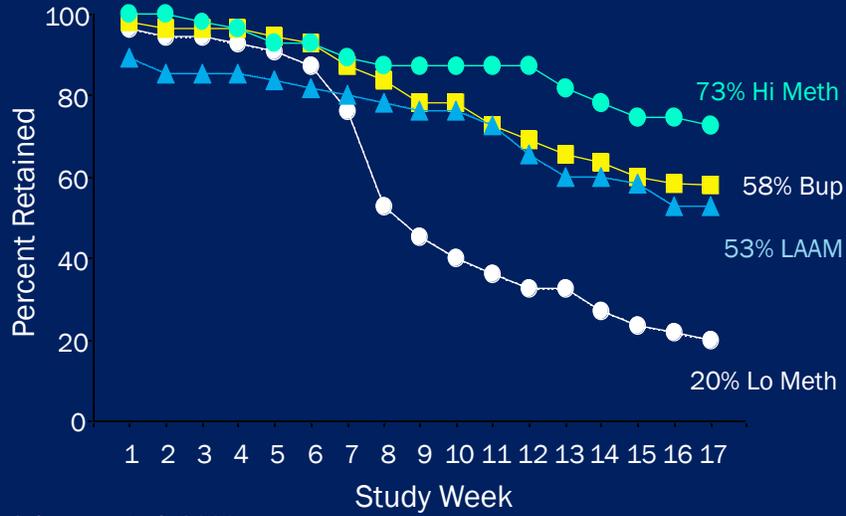
Buprenorphine treatment associated with viral suppression.

Mean Heroin Craving with buprenorphine : 16 Week Completers



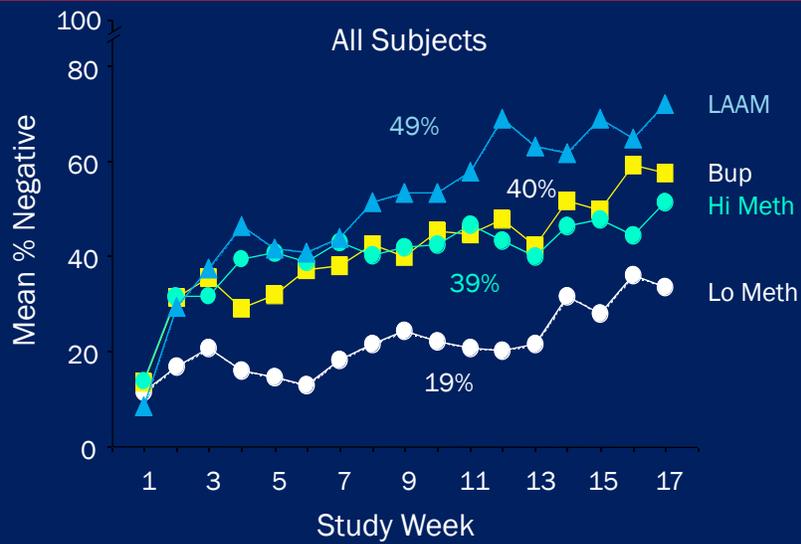
(Ling et al., 1998)

## BUPRENORPHINE, METHADONE, LAAM: TREATMENT RETENTION



Johnson et al, 2000

## BUPRENORPHINE, METHADONE, LAAM: OPIOID URINE RESULTS



## SAFETY CONSIDERATIONS IN MAINTENANCE PHARMACOTHERAPIES

Avoid sedation and respiratory depression (stay within tolerance, avoid overdose risk)

Minimize side effects of constipation, sweating, hypogonadism

Alertness to potential medication interactions, QT/cardiac risk, other sedatives.

Methadone has QT warnings.

Minimize diversion, accidental ingestion or dosing errors

## SAFETY CONSIDERATIONS SPECIFIC TO EACH PHARMACOTHERAPY

	Methadone	Buprenorphine	Naltrexone	IM Naltrexone
Induction risk	<b>Overdose in first week</b>	<b>Precipitated withdrawal</b>	1 week abstinent, may require residential.	1 week abstinent, may require residential.
Med. Interaction	QT drugs Sedatives	Sedatives Opioids	Opioids	Opioids
Ongoing use	Constipation Hypogonadism	Constipation Hypogonadism (less than MMT)	<b>Lowered tolerance (risk of overdose)</b>	Injection site reactions <b>Lowered tolerance</b>
Logistics	Regulated clinic	X number, SL admin	Adherence	Injection skill, cost

## MAT AND OVERDOSE

Respiratory depression risk increased with:

- higher dose of full opioid agonist
- addition of sedative/hypnotic to agonist or partial agonist, including alcohol.
- lung disease or sleep apnea
- lowered tolerance (institutional, or antagonist induced)

Naloxone co-prescribing recommended

Partial agonist generally safer

Special risk of overdose: fentanyl contamination of street drugs

### OPIOID AGONIST DRUG EFFECTS: REDUCED WHEN PARTIAL AGONIST IS USED

Acute Use Effects			
Euphoria	Vomiting	Constricted Pupils	Depressed Respiration
Drowsiness	Decreased Pain Sensation	Decreased Awareness	Decreased Consciousness

Large Dose Acute Effects			
Non-Responsive	Pinpoint Pupils	If Severe Anoxia Pupils May Dilate	Bradycardia & Hypotension
Skin Cyanotic	Skeletal Muscle Flaccid	Pulmonary edema in ~50%	Slow or Absent Respiration

Chronic Use Effects			
Physical dependence	Hypogonadism	Sweating	Reduction in bowel movement

## Buprenorphine Induction

- **Goals of induction to maintenance treatment**
  - **discontinue or markedly reduce use of other opioids,**
  - **no cravings, ongoing control of withdrawal symptoms**
  - **minimal/no side effects**
  - **Protect against ravages of needle-related illness**
  - **Improve ability to function, quality of life**

## Buprenorphine Induction First dose

- **Patients dependent on short-acting opioids (e.g.:heroin/oxycodone/hydrocodone)**
  - **Instruct patients to abstain from any opioid use for 12 hours prior to induction visit (so they are in mild-moderate withdrawal at induction visit)**
  - **Use opioid withdrawal scale (COWS > 7 is sometimes used) to document and assess severity of withdrawal and to track the patient's response to first day's dose**

## Buprenorphine Induction – Day 1

- **Patients dependent on long-acting opioids (e.g. methadone)**
  - Patients should have dose decreases until they are down to  $\leq 40$  mg/d of methadone, for a week
  - Begin induction 24-36 hours after last dose of methadone
  - Give no further methadone once buprenorphine induction is started
  - Procedure is then the same as for short-acting opioids
  - *Key is to observe objective withdrawal signs (for example pupillary size)*
    - e.g.: expect first day's dose to be up to 8 mg SL

### Poll:

- Do you have a protocol for transfer from methadone to buprenorphine?
  - Yes
  - No or not yet

### Clinical Opiate Withdrawal Scale (COWS)

#### Flow-sheet for measuring symptoms over a period of time during buprenorphine induction.

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____	Date: _____
Buprenorphine induction: Enter scores at time zero, 30min after first dose, 2 h after first dose, etc. Times: _____	
Resting Pulse Rate: (record beats per minute) Measured after patient is sitting or lying for one minute	
0 pulse rate 80 or below	
1 pulse rate 81-100	
2 pulse rate 101-120	
4 pulse rate greater than 120	
Sweating: over past ½ hour not accounted for by room temperature or patient activity.	
0 no report of chills or flushing	
1 subjective report of chills or flushing	
2 flushed or observable moistness on face	
3 beads of sweat on brow or face	
4 sweat streaming off face	

These are only the first two items on the scale, for the slide

### Poll:

- What **minimum** COWS score have you set for giving the first dose of buprenorphine?
  - Seven or lower
  - 8
  - 9-11
  - 12-14
  - Don't use COWS
  - Haven't decided

## Buprenorphine Induction – Day 1

- **When withdrawal is documented, give first dose: 2-8 mg sublingual buprenorphine/naloxone**
- **Note: primary use of buprenorphine alone tablet is in pregnancy , or for observed, in-clinic doses**
- **Monitor in clinic for up to 2 hours after first dose, or see next day for possible dose adjustment**

## Poll:

- What induction dose do you most commonly use?
- 2mg
- 4mg
- 8mg
- Not doing inductions yet

## Buprenorphine Induction – Day 1

- If precipitated withdrawal occurs consider:
  - giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal; can give medications for withdrawal symptoms if needed (recommended)
  - or
  - stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day

## Buprenorphine Stabilization / Maintenance

- Give dose daily until stabilized
- Usual administration of buprenorphine/naloxone dosing is daily , although analgesic effect is shorter.
- Once stabilized, patient can take dose daily or can be shifted to alternate day dosing (e.g., every 48-72 hours) if monitored dosing is desired
- Increase dose on dosing day by amount not received on other days (e.g., if on 8 mg/d, switch to 16/16/24 mg MWF) for someone who needs observed dosing.

## DOSE RESPONSE, BUPRENORPHINE

*Drug Alcohol Depend.* 2014 November 1; 0: 1-11

Greenwald et al: *Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy.*

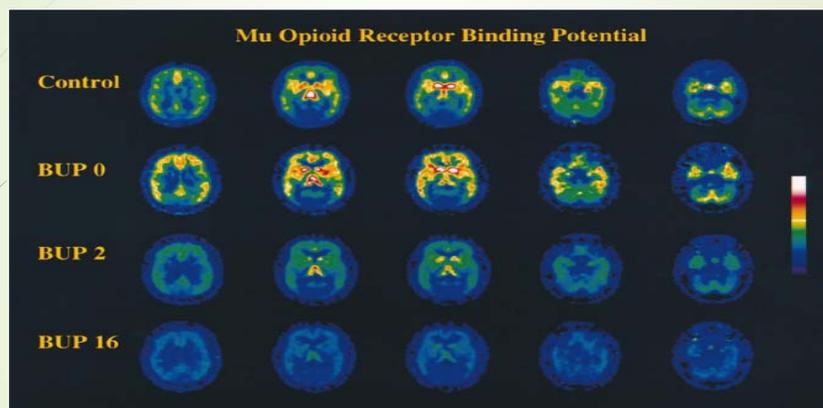
Scientific review of mu opioid receptor availability studies, correlated to usual buprenorphine SL doses and clinical presentation of opioid use disorder.

Withdrawal suppression may occur at 4mg, blockade of reinforcing effects of heroin or other opioids occurs around 16mg, for persons who use larger than usual amounts, would require higher doses.

(This review article presented a science-based argument against dose caps and rigid dose regimens.)

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## Buprenorphine Binding mu Receptors



- Buprenorphine blocks opioid full mu agonist binding
- Zubieta et al [U Mich] *Neuropsychopharmacology* 23:326-334, 2000

## MAT DOSE DOESN'T CORRELATE WITH PRESCRIPTION OPIOID EQUIVALENCE TABLES: A SAFETY CONCERN

Drug Alcohol Rev. 2016 Jun 7, Nielsen et al: *Opioid agonist doses for oxycodone and morphine dependence: Findings from a retrospective case series.*

Retrospective case series of 44 prescription opioid use disorder patients. (69% reported a pain condition)

Calculated oral morphine equivalents at entry then compared buprenorphine or methadone dose required.

MAT doses varied and did not correlate with oral prescription opioids used prior to entry.

## What is a diversion control plan?

- Structured approach to preventing and addressing diversion
- Usually includes a range of observation, including directly observed dosing.
- Usually includes toxicology and buprenorphine testing.
- Usually includes a patient agreement about behavior, and refill policy.
- Often has a variety of levels of concern: selling versus stockpiling or sharing, early refills versus late refills, presence vs absence of buprenorphine in urine, etc.
- (Usually not completely evidence-based.)

## Evidence base, review of literature on diversion in MAT.

- ▀ Review of diversion literature
- ▀ 'Buprenorphine diversion' yielded 169 results in pubmed.
- ▀ Several articles discussed in this slide set on topics of:
  - ▀ Statistics and variability by formulation and setting
  - ▀ Risks and benefits of diversion
  - ▀ Types of 'diversion' – definition variable
  - ▀ Patient and clinician attitudes about diversion

## Diversion during observed dosing, motivation and method of diversion

*Winstock et al, Journal of Addictive Diseases, 2009:*

Interviews upon suspected diversion after observed dosing, 71 episodes among 52 clients in public MAT programs in Sydney Australia, 2005-6. (all were tablets)

35/71 diverted by removal from mouth, usually to hand or clothing,

28/71 diverted by moving tablet to other place in mouth.

4/71 diverted by leaving before dose dissolved

Plans:

15/71: stockpiling for later use

11/71: discarding

5/71: giving to another person

## Motivation for diversion when given:

*Winstock et al, Journal of Addictive Diseases, 2009:*

Dose too high, Stockpile to manage withdrawal, want to split dose, divert to friend, unpleasant taste or burning, fear hard to get off, too long to dissolve, peers standing there expecting, didn't want dose that day, wanted self detox.

**Patients recommended crushed tablets and mouth rinsing as ways to manage diversion.**

## Statistics, film vs tablet, bup vs bnx

- *Lavonas et al, Journal of Substance Abuse Treatment 47 (2014) 27-34:*
- "Combination film rates were significantly less than rates for either tablet formulation in all programs. ..."
- The availability-adjusted **injection abuse rate** for single ingredient buprenorphine tablets was 20 times the injection abuse rate for the combination film, and combination tablet injection was reported at a supply-adjusted rate 2.5 times that of combination film."



## Statistics on risk: overdose

- ▶ Paone et al, [Drug Alcohol Depend.](#) 2015 :
- ▶ Review of blood samples from 98 unintentional overdose decedents in New York City in 2013.
- ▶ All had multiple substances. Only 2 of 98 had buprenorphine metabolites.



## Discussion and questions/sharing

- ▶ Does anyone have a goal/protocol for transferring stable patients to primary care?
- ▶ Do you crush tablet?
- ▶ Do you choose formulations that are available in primary care?
- ▶ What is your observed dose protocol for dispensing?
- ▶ Is anyone using three times weekly observed dosing?