MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Buprenorphine 101

Laura G. Kehoe, MD, MPH, FASAM
Medical Director, MGH Substance Use Disorder Bridge Clinic
Assistant Professor of Medicine
Harvard Medical School

Disclosures

I have the following relevant financial relationship with a commercial interest to disclose

Medical Consultant:

- MAP Health Management Peer Recovery Specialists
- PATH CCM
- MCSTAP Massachusetts Consultation Service for the Treatment of Addiction and Pain (funded by Massachusetts government)

Post Data 2000

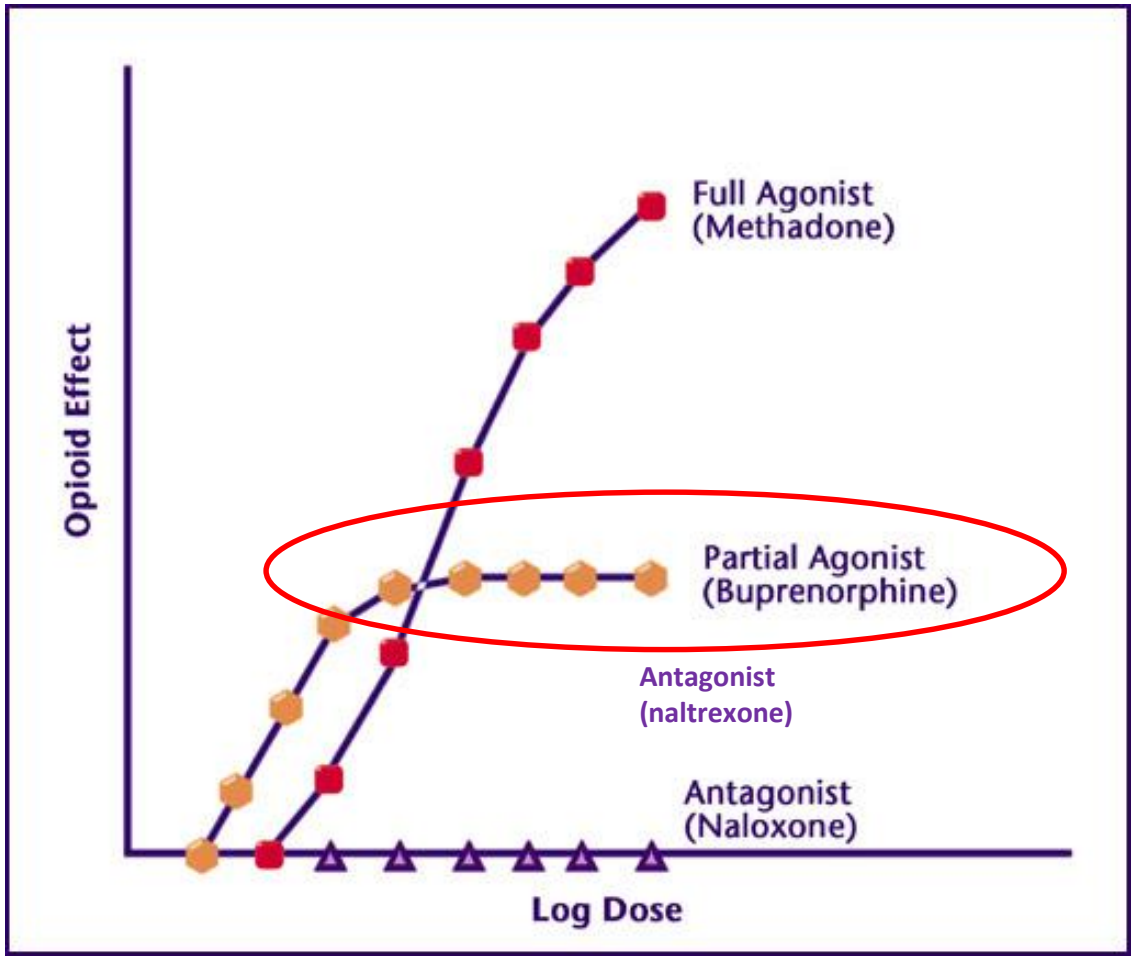
First patient I treated with buprenorphine:

Myths

- Buprenorphine precludes “real” sobriety
- Short term treatment is ok
- All patients need an in-office induction
- All patients need a full physical and lab work prior to starting medication
- No one should ever be Rx above 16 mg daily
- All Rx need to be hard copies, cannot be called in
- Everyone must engage in therapy if Rx buprenorphine
- Buprenorphine is absolutely contraindicated if using other substances
- Everyone must be moved to a higher level of care if using other substances or not engaging
- Teaching about or encouraging safe injection practice may trigger more use and is contradictory to medication management
- Rx buprenorphine takes too much time/is too difficult

Martin 2018, Gjersin L 2013,Feillen DA 2013, Dugosh 2010

Buprenorphine's Pharmacology Imparts Efficacy and Safety



Buprenorphine

* Naloxone is not the culprit

Initiating Buprenorphine

- Must be in mild to moderate withdrawal before taking initial dose
- This can be done in-office or at home
- Home inductions safe, patient centered, more efficient
- Many patients have taken buprenorphine before and can guide us

Lee, Journal Addiction Med, 2014

A Guide for Patients Beginning Buprenorphine Treatment at Home

Before you begin you want to feel very sick from your withdrawal symptoms

It should be at least . . .

- 12 hours since you used heroin/fentanyl
- 12 hours since snorted pain pills (Oxycontin)
- 16 hours since you swallowed pain pills
- 48-72 hours since you used methadone

You should feel at least three of these symptoms . . .

- Restlessness
- Heavy yawning
- Enlarged pupils
- Runny nose
- Body aches
- Tremors/twitching
- Chills or sweating
- Anxious or irritable
- Goose pimples
- Stomach cramps, nausea, vomiting or diarrhea

Once you are ready, follow these instructions to start the medication

DAY 1:

8-12mg of buprenorphine

Most people feel better the first day after 8-12mg. (Dosing depends on how early on the first day you started)

Step 1.

Take the first dose	Wait 45 minutes
4mg	

- Put the tablet or strip under your tongue
- Keep it there until fully dissolved (about 15 min.)
- Do NOT eat or drink at this time
- Do NOT swallow the medicine

Step 2.

Still feel sick? Take next dose	Wait 6 hours
4mg	

Most people feel better after two doses = 8mg

Step 3.

Still uncomfortable? Take last dose	Stop
4mg	

- Stop after this dose
- Do not exceed 12mg on Day 1

DAY 2:

up to 16mg of buprenorphine

Take up to a 16mg dose

Most people feel better with up to a 16mg dose

16mg

Repeat this dose until your next follow-up appointment

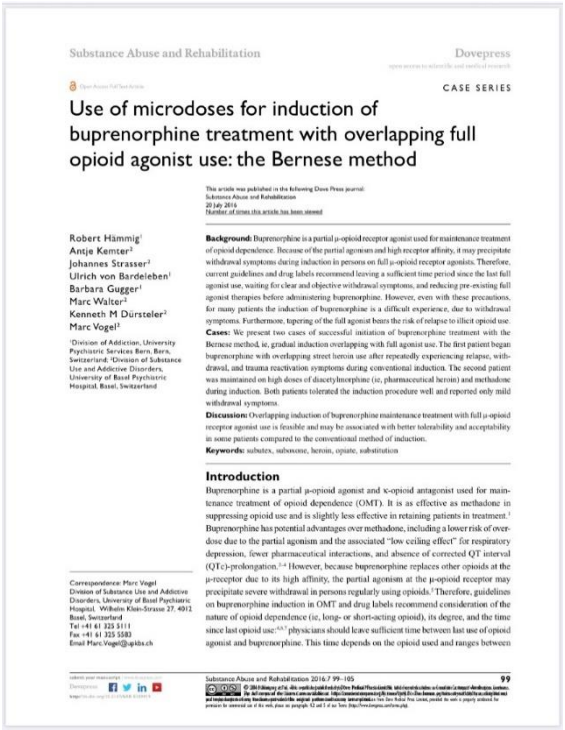
If you develop worsening symptoms while starting buprenorphine before your scheduled outpatient appointment return to the emergency department

Note: This is a modified version of a NIDA guidance document

Buprenorphine Microdosing: the "Bernese Method"

Hypothesis:

- Repeated microdoses of buprenorphine with sufficient dosing intervals should not precipitate withdrawal
- Buprenorphine will accumulate at the receptor because of the long receptor binding time
- Over time, an increasing amount of a full μ-agonist will be replaced by buprenorphine at the opioid receptor
- Overlapping induction of buprenorphine with ongoing use of illicit opioid (fentanyl) or full μ-agonist should be possible without precipitating severe opioid withdrawal



Substance Abuse and Rehabilitation Dovepress

CASE SERIES

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

Robert Hämmig[1]
Antje Kemter[2]
Johannes Strasser[2]
Ulrich von Bardeleben[1]
Barbara Gugger[1]
Marc Walter[2]
Kenneth M Dürsteler[2]
Marc Vogel[2]

[1]Division of Addiction, University Psychiatric Services Bern, Bern, Switzerland; [2]Division of Substance Use and Addictive Disorders, University of Basel Psychiatric Hospital, Basel, Switzerland

Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Cases: We present two cases of successful initiation of buprenorphine treatment with the Bernese method, ie, gradual induction overlapping with full agonist use. The first patient began buprenorphine with overlapping street heroin use after repeatedly experiencing relapse, withdrawal, and trauma reactivation symptoms during conventional induction. The second patient was maintained on high doses of diacetylmorphine (ie, pharmaceutical heroin) and methadone during induction. Both patients tolerated the induction procedure well and reported only mild withdrawal symptoms.

Discussion: Overlapping induction of buprenorphine maintenance treatment with full μ-opioid receptor agonist use is feasible and may be associated with better tolerability and acceptability in some patients compared to the conventional method of induction.

Keywords: subutex, suboxone, heroin, opiate, substitution

Introduction

Buprenorphine is a partial μ-opioid agonist and κ-opioid antagonist used for maintenance treatment of opioid dependence (OMT). It is as effective as methadone in suppressing opioid use and is slightly less effective in retaining patients in treatment.[1] Buprenorphine has potential advantages over methadone, including a lower risk of overdose due to the partial agonism and the associated "low ceiling effect" for respiratory depression, fewer pharmaceutical interactions, and absence of corrected QT interval (QTc)-prolongation.[2–4] However, because buprenorphine replaces other opioids at the μ-receptor due to its high affinity, the partial agonism at the μ-opioid receptor may precipitate severe withdrawal in persons regularly using opioids.[5] Therefore, guidelines on buprenorphine induction in OMT and drug labels recommend consideration of the nature of opioid dependence (ie, long- or short-acting opioid), its degree, and the time since last opioid use:[6,7] physicians should leave sufficient time between last use of opioid agonist and buprenorphine. This time depends on the opioid used and ranges between

Correspondence: Marc Vogel
Division of Substance Use and Addictive Disorders, University of Basel Psychiatric Hospital, Wilhelm Klein-Strasse 27, 4012 Basel, Switzerland
Tel +41 61 325 5111
Fax +41 61 325 5583
Email Marc.Vogel@upkbs.ch

Substance Abuse and Rehabilitation 2016:7 99–105 99

Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil. 2016;7:99–105.

An Extensive Assessment is Not Necessary

NYS Best Practices :

- Assess the patient's history to establish presence of OUD, other drug use, history of drug treatment and significant medical and psychiatric history.
- Conduct a focused physical examination, refer for a physical exam, or get a record of a recent one.
- Order relevant laboratory tests – but results are not required to initiate prescribing.
- Check the state prescription drug monitoring program database
- Initiate prescribing: SAMHSA guidance now supports both in-office and unsupervised induction.

Policy changes for prescribing buprenorphine during pandemic

Prior to COVID 19

- Prescribed through pharmacies in outpt settings
- DATA 2000, limited clinicians with bupe waivers that required additional training and federal registration
- Limited number of patients to treat
- **In person evaluation for initial dose**

Since COVID 19

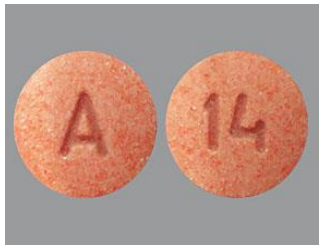
- **3/17/20: Buprenorphine initiation via telehealth without in person visit**
- Follow up can be via phone

Buprenorphine Can and Should Be Prescribed for Relapse Prevention

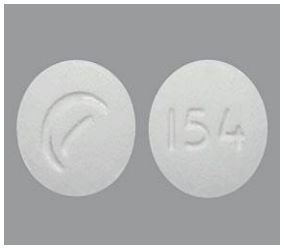
- Consider if good evidence of history of opioid use disorder and high risk for relapse
- Start lower dose and increase more slowly
  - 2 mg reasonable starting dose
- Examples:
  - Recently released from prison or involuntary commitment
  - Leaving a sober house or halfway house

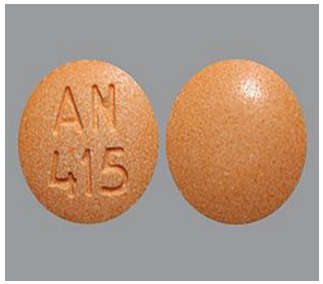

KEEP
CALM
AND
LISTEN TO
YOUR PATIENTS

Buprenorphine/naloxone

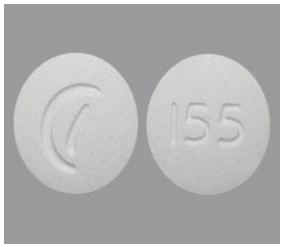


2mg/0.5mg





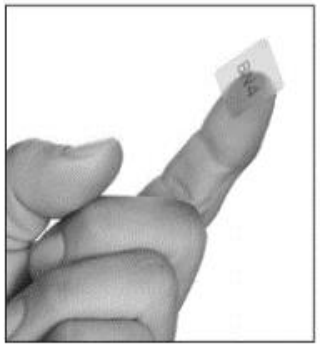
8mg/2mg

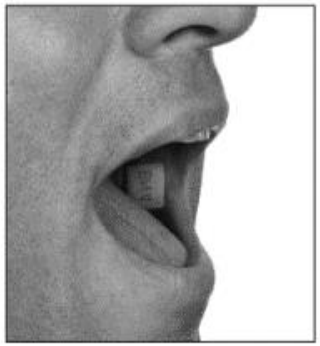


Buprenorphine/naloxone Sublingual Tablets (Zubsolv)

- Available doses (BUP/NX): 1.4 mg / 0.36 mg; 5.7 mg / 1.4 mg
- Recommended maintenance dose: 11.4 mg/ 2.8 mg
- Different flavor

Buccal Film (Bunavail)





Available dosages (BUP/NX): 2.1 mg / 0.3 mg; 4.2 mg/0.7 mg; 6.3 mg/ 1.0mg

Recommended maintenance dose: 8.4mg / 1.4mg

Subcutaneous XR Buprenorphine (Sublocade)

- Monthly
- Must have tolerated SL buprenorphine
- Prior Authorization
- Patient Preference guides decision
- Particularly helpful if trouble with SL taste, adherence, travel

XR Buprenorphine

THE LANCET
Volume 393, Issue 10173, 23 February–1 March 2019, Pages 778-790

Articles

Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

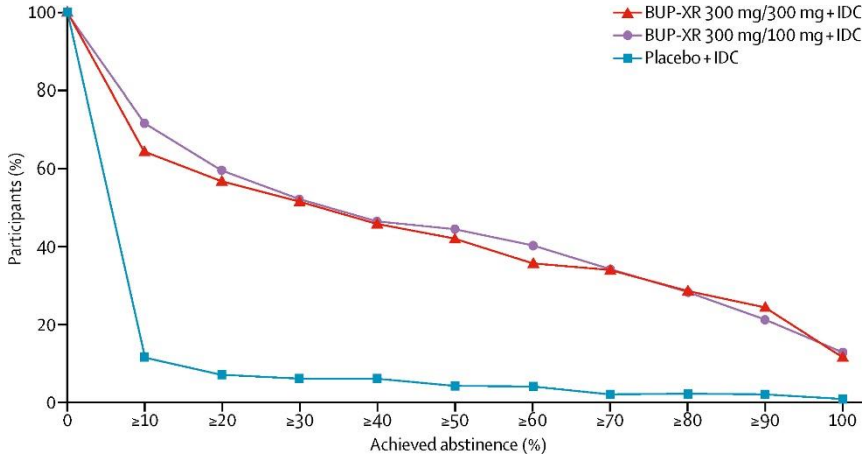
Barbara R Haight PharmD [a], Susan M Learned MD [a], Celine M Laffont PhD [a], Paul J Fudala PhD [a], Yue Zhao MD [a], Amanda S Garofalo MSHS [a], Prof Mark K Greenwald PhD [b], Vijay R Nadipelli MS [a], Prof Walter Ling MD [c], Christian Heidbreder PhD [a]

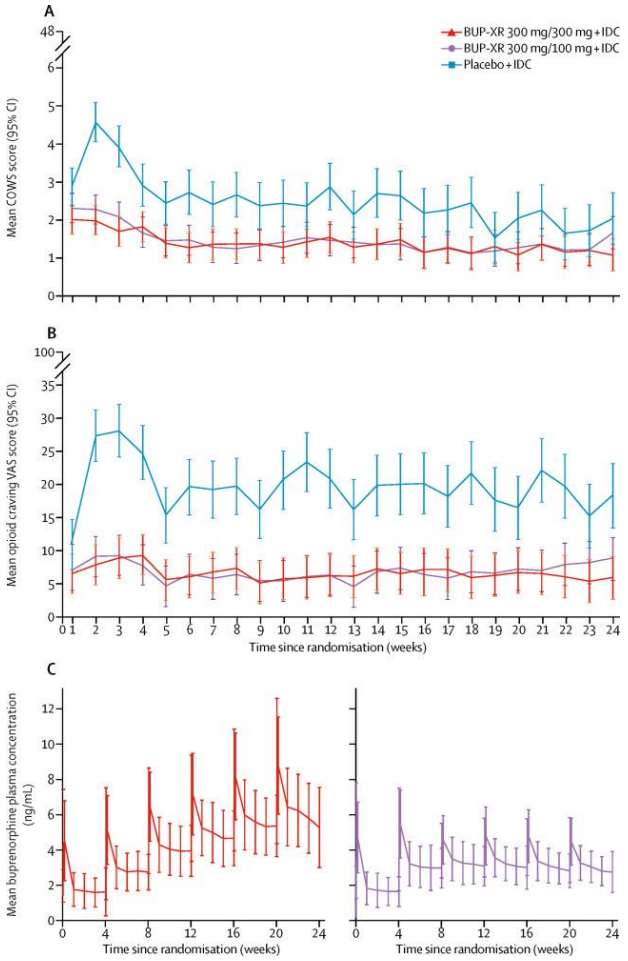
Placebo-controlled 3 arm trial (N = 504)

- Compared:
  - BUPE XR 300mg/100 mg (2 x 300 mg, then 4 x 100 mg
  - BUP XR 300mg/300mg (6 x 300 mg)
  - Placebo
- 2 week open label run up with Bupe film 8-24 mg/day
- Mean participants % abstinent
  - (defined as percentage neg urine samples and self report weeks 5-24)
  - BUP XR 300mg/300 mg (41.3%)
  - Bup XR 300mg/100 mg (42.7%)
  - Placebo (5%)

Haight, 2019

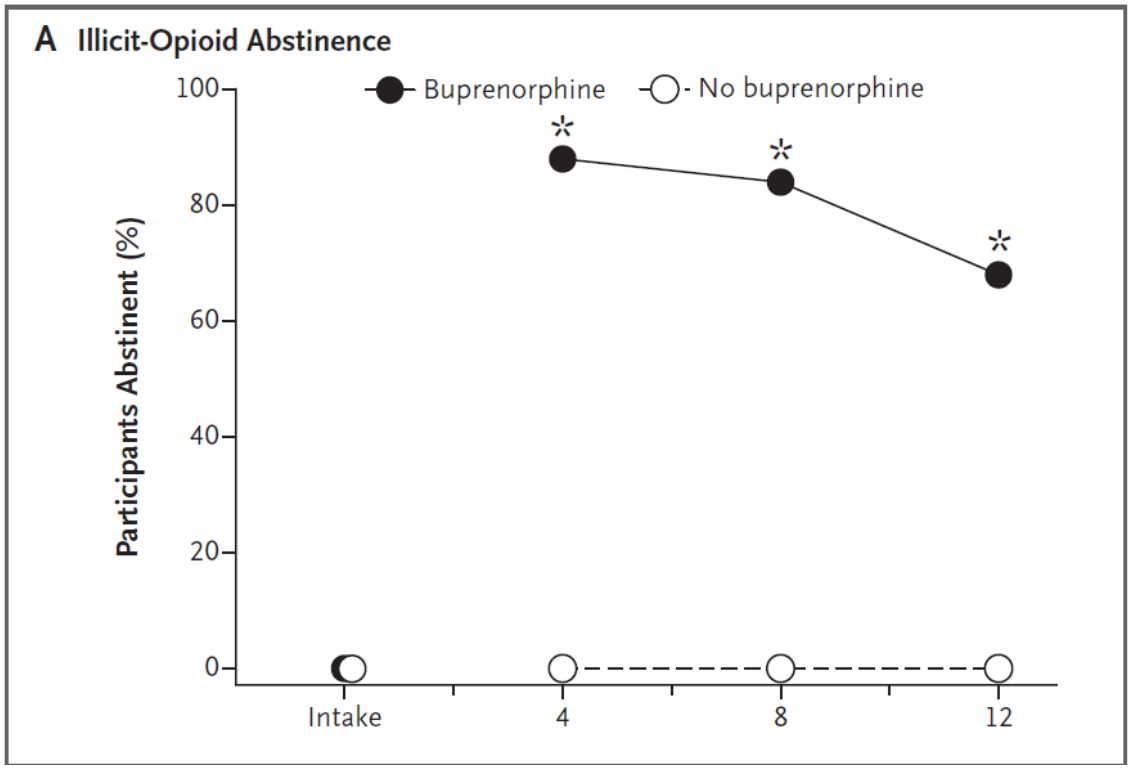
XR Buprenorphine





Haight, 2019

Interim Buprenorphine Improves Outcomes



Sigmon et al. N Engl J Med. 2016 Dec 22;375(25):2504-2505.

Hospitalized Patients

- Initiating buprenorphine vs detox:
  - Bupe: 72.2% enter into treatment after discharge
  - Detox : 11.9% enter treatment after discharge

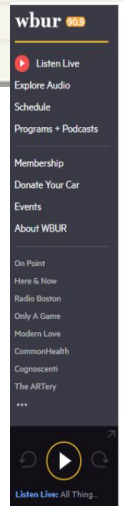
J Gen Intern Med. Aug 2010; 25(8): 803–808; JAMA Intern Med 2014 Aug;174(8):1369-76.)

ED Initiated Buprenorphine

- 78% vs 37% engaged in buprenorphine treatment
- Fewer days of self-reported opioid use

Table 2. Baseline and 30-Day Secondary Outcome Measures Among Opioid-Dependent Patients Treated in the Emergency Department[a]

	Referral	Brief Intervention	Buprenorphine	*P* Value[b]
Days of Self-reported Illicit Opioid Use in the Past 7 Days, Mean (95% CI)				
Baseline	5.4 (5.1-5.7)	5.6 (5.3-5.9)	5.4 (5.1-5.7)	
30 d	2.3 (1.7-3.0)	2.4 (1.8-3.0)	0.9 (0.5-1.3)	



MGH Becomes 1st Mass. ER To Offer Addiction Medication, Maps Seamless Path To Recovery

A clean-cut man in his early 30s buttons the jacket of his tailored suit as he strides to the head of a conference table at Massachusetts General Hospital.

What's the OD risk on Buprenorphine?

- Very low
- Partial agonist, ceiling effect, risk respiratory depression low
- OD Deaths from buprenorphine low
    - most combined with high dose IV benzos
    - children who got into it
- OD risk with illicit opioid very high

Ling 2002, JSAT

What About Diversion?

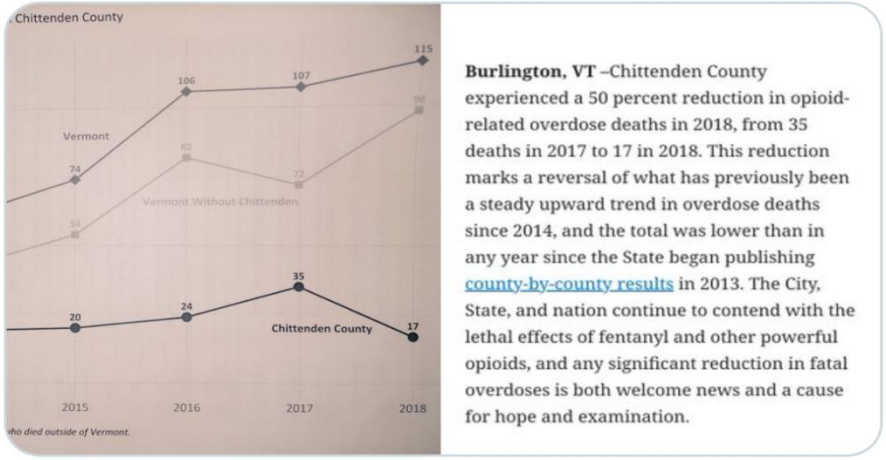
- Happens
  - Poor access to care
  - Sub-therapeutic dosing
  - Helping others
  - Can be a way to help get people into care
  - Not to get high
- Best way to decrease diversion is to increase access to care
- Short Rx and closer interval fu
- Open communication

Fox et al. J Subst Abuse Treat. 2015 Jan;48(1):112-6
Johnson Int J Drug Pol 2014
Launonen Int J Drug Pol 2015
Monico JSAT 2015

Brandon del Pozo @Brandonde... · Feb 14

What's the point of naloxone, buprenorphine, a syringe exchange, no wait for treatment, not arresting for unprescribed addiction meds, putting treatment before arrests, & using a CompStat approach?

The City of Burlington saw a 50% decrease in opioid overdose deaths in 2018.



Burlington, VT –Chittenden County experienced a 50 percent reduction in opioid-related overdose deaths in 2018, from 35 deaths in 2017 to 17 in 2018. This reduction marks a reversal of what has previously been a steady upward trend in overdose deaths since 2014, and the total was lower than in any year since the State began publishing county-by-county results in 2013. The City, State, and nation continue to contend with the lethal effects of fentanyl and other powerful opioids, and any significant reduction in fatal overdoses is both welcome news and a cause for hope and examination.

22 308 698

Critical Need for Flexible Care Models

- Individuals using SEPs report barriers to accessing buprenorphine treatment
- Those using illicit buprenorphine describe interest in treatment but barriers to access
- Experiencing barriers associated with preference to receive care in harm reduction agency

Barriers include:

- Stigma
- Where? How? Balancing competing priorities
- Transportation, childcare, work, inability to pay
- Complicated registration and multi-step intake process
- Difficulty articulating needs
- *Legacy of past negative experiences with treatment providers* → ***Conditioned not to trust us***

Edland-Gryt M. Int J Drug Policy. 2013 May;24(3):257-64.; Mofizul Islam Fox et al. Subst Abus. 2015; 36(2): 155–160.

Critical Need for Flexible Care Models

"I'm all over the place… Appointments are really hard for me. And I didn't want to not take the medicine, so I've taken it every day up until now… It's just really hard setting up appointments and then trying to go about things the way that other people would want me to do at the hospital."

Wakeman, Kehoe, Snow et al. J Subst Abuse Treat. 2019 Dec; vol 107:1-7.

What about Benzodiazepines?

"Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications ***buprenorphine and methadone should not be withheld from patients taking benzodiazepines*** or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, ***the harm caused by untreated opioid addiction can outweigh these risks.***"

- FDA Drug Safety Communication, 9/20/17

Dose Needs to Be Therapeutic

- natural experiment demonstrating the effect of an imposed decrease in buprenorphine dose
- pseudo-experimental group demonstrated worsened clinical outcomes after a dose limit of 16 mg/day was imposed upon them
- those rx >16 mg/day had greater retention

The Effect of a Payer-Mandated Decrease in Buprenorphine Dose on Aberrant Drug Tests and Treatment Retention Among Patients with Opioid Dependence

Anthony J Accurso [1], Darius A Rastegar [2]

Affiliations + expand

PMID: 26639639 DOI: 10.1016/j.jsat.2015.09.004

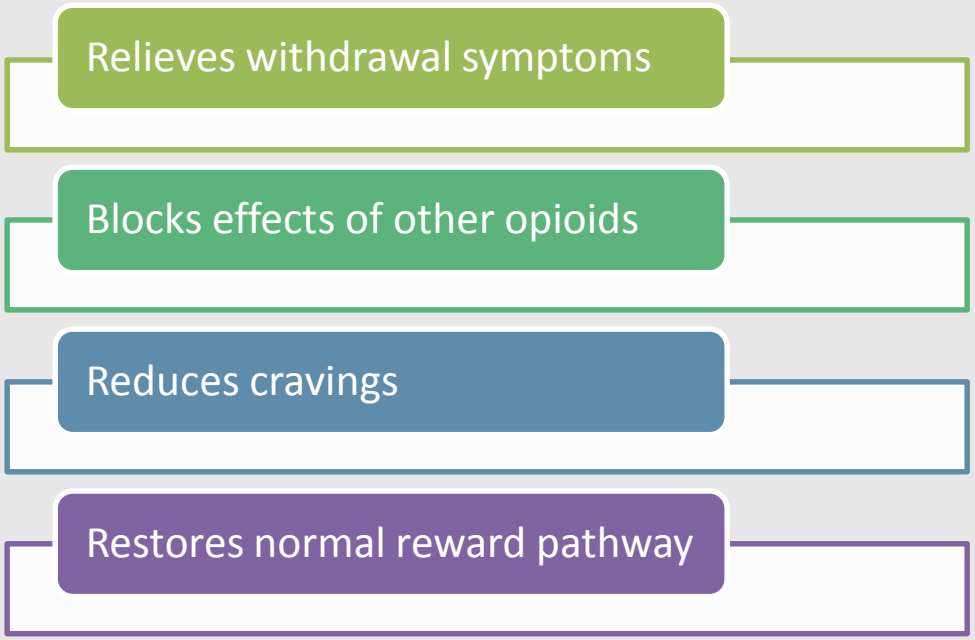
Abstract

Background: The optimal dose for office-based buprenorphine therapy is not known. This study reports on the effect of a change in payer policy, in which the insurer of a subset of patients in an office-based practice imposed a maximum sublingual buprenorphine dose of 16 mg/day, thereby forcing those patients on higher daily doses to decrease their dose. This situation created conditions for a natural experiment, in which treatment outcomes for patients experiencing this dose decrease could be compared to patients with other insurance who were not challenged with a dose decrease.

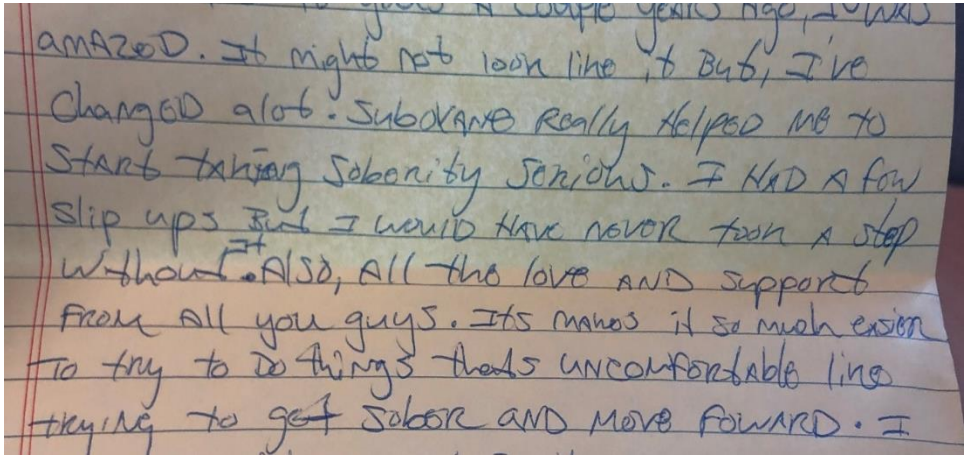
Methods: Subjects were 297 patients with opioid use disorder in a primary care practice who were prescribed buprenorphine continuously for at least 3 months. Medical records were retrospectively reviewed for urine drug test results and treatment retention. Rates of aberrant urine drug tests were calculated in the period before the dose decrease and compared to rate after it with patients serving as their own controls. Comparison groups were formed from patients with the same insurance on buprenorphine doses of 16 mg/day or lower, patients with different insurance on 16 mg/day or lower, and patients with different insurance on greater than 16 mg/day. Rates of aberrant drug tests and treatment retention of patients on 16 mg/day or less of buprenorphine were compared to that of patients on higher daily doses.

Accurso AJ, Rastegar DA. J Subst Abuse Treat. 2016 Feb

At therapeutic doses, buprenorphine…

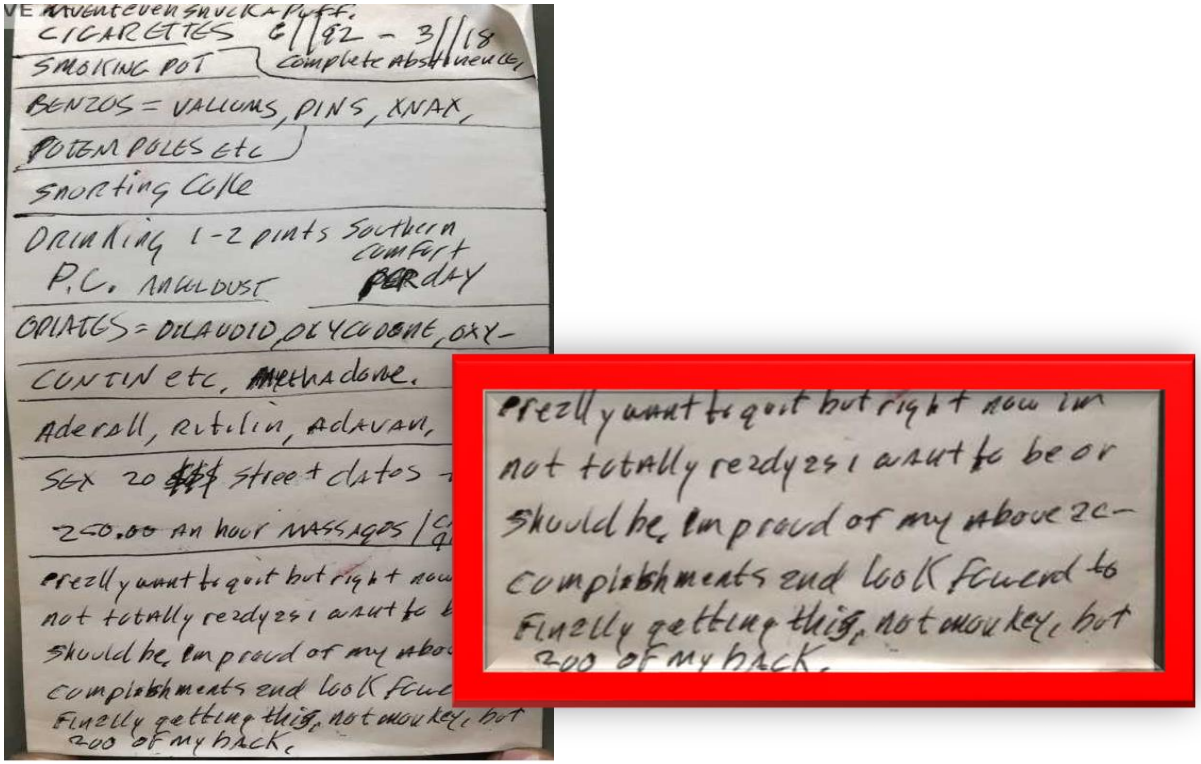


Functional Status and QOL as Markers of Success



Letter from MGH Bridge Clinic patient shared with permission, 2018

Understanding Ambivalence



Letter from MGH Bridge Clinic patient shared with permission, 2017

Buprenorphine Wrap Up

Thank You!

@drlaurakehoe

lgkehoe@mgh.harvard.edu