SUBOXONE (BUPRENORPHINE/NALOXONE)

—

MANAGING PAIN IN THE FACE OF SUBSTANCE USE DISORDER

Nathan Dewey, MD
UVA Health
Palliative Medicine Fellow

CREDITS & INSPIRATION

- Thokozeni Lipato, MD
- Nat Timmins, MD
- Leslie Blackhall, MD

LEARNING OBJECTIVES

- Describe the basic pharmacology of Suboxone to understand its role and nuances
- Describe two methods of Suboxone induction
- Describe strategies to treat complications while on Suboxone

CONFLICTS OF INTEREST

None

SUBOXONE BASICS

- Contains buprenorphine and naloxone in a 4:1 ratio
- Buprenorphine component is a high dose
  - Provides good analgesia in opioid-tolerant patients
  - Requires a careful induction process
- Naloxone component deters IV misuse of the medication
- Taken sublingually as a film or a tablet
- Dosed TID or QID for pain
- Expensive
  - May be a few hundred dollars per month without insurance
  - Medicaid typically covers amounts up to 24-6 mg per day
- Hepatic metabolism for both drug components
  - Careful use in moderate hepatic impairment, avoid use in severe hepatic impairment (Child-Pugh class)
- Requires an X-waiver to prescribe for OUD, not for pain*

BUPRENORPHINE BASICS

- Partial mu-opioid receptor agonist
  - Provides analgesia while limiting side effects including respiratory depression and psychomimetic/dysphoric/sedating effects
  - Tolerance to its analgesic effect has not been observed
  - Limited abuse potential
- High mu-opioid receptor affinity
  - Inhibits the action of other opioids
  - Adjunct full-mu agonists can be used in high doses with buprenorphine for severe pain episodes
- Sublingual and parenteral bioavailability
- Metabolized by the liver
- Can elevate AST/ALT, requires monitoring

NALOXONE BASICS

- Mu-opioid receptor antagonist with high affinity
  - Blocks the action of other opioids when taken parenterally
- Parenteral bioavailability, poor sublingual bioavailability
  - Does not affect proper use of Suboxone, but deters IV misuse
- Metabolized by the liver
  - High sublingual bioavailability in severe hepatic impairment

WHY USE SUBOXONE FOR PAIN?

Poor analgesic effect from full mu-opioid agonists

Substance use disorders (opioids or other substance misuse)

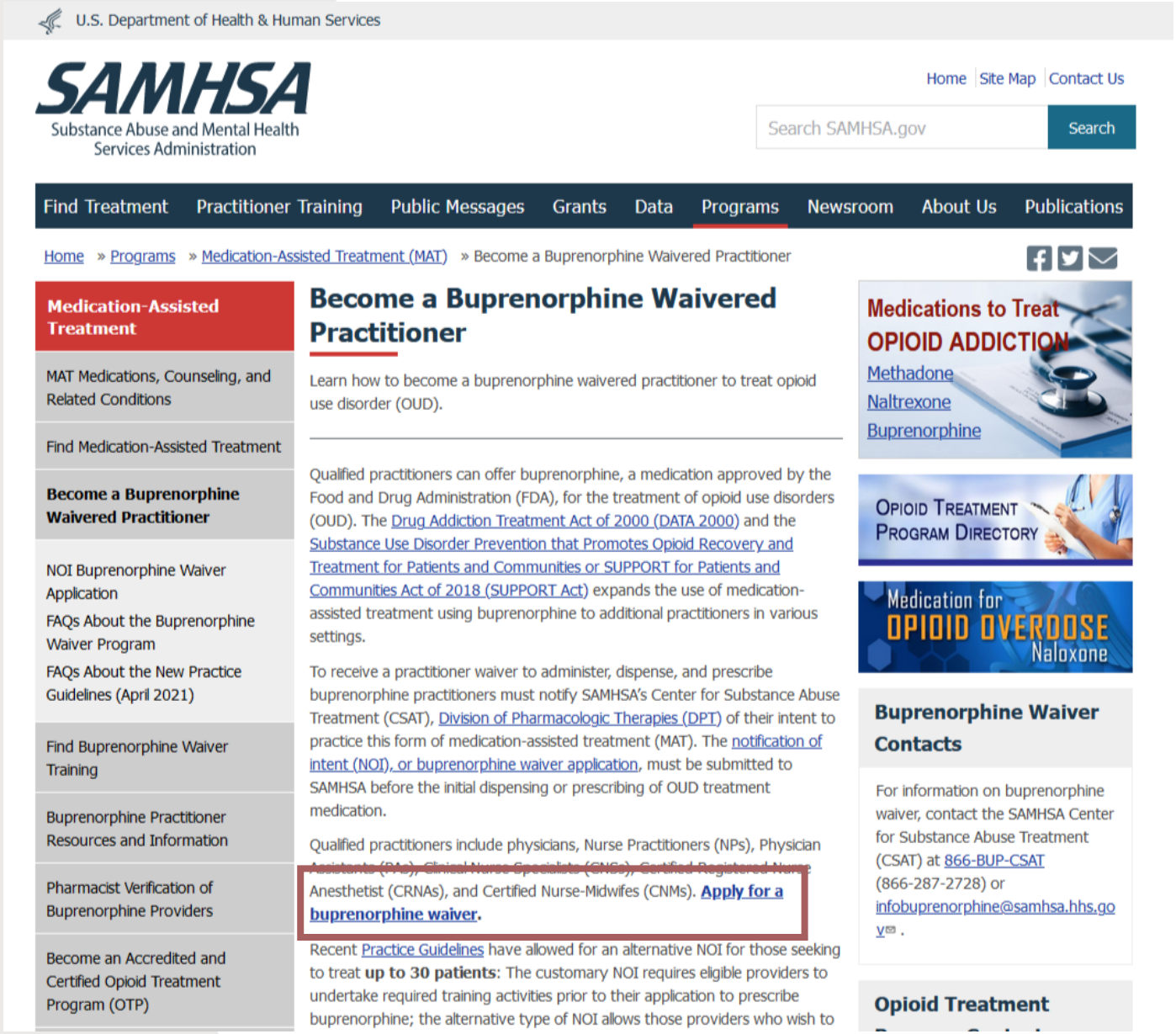
Side effect burden from full mu-opioid agonists

SUBOXONE X-WAIVER

- VERY brief application process

https://www.samhsa.gov/medication-assisted-treatment/become-buprenorphine-waivered-practitioner

- Requires your medical license state, medical license number, DEA number, and primary practice address
- 30 patients or less, no training session



DOSE EQUIVALENCY ESTIMATE

Parenteral MEDD (morphine equivalent daily dose)	Oral MEDD, converted using a 1:2.5 ratio	Methadone equivalent daily oral dose	Buprenorphine equivalent daily sublingual tablet dose
40-60	100-150	20-30	4
80	200	40	8
100-120	250-300	50-60	16

MU-OPIOID RECEPTOR AFFINITY

Drug	K_i (nM)	Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Hydrocodone	41.58	Butorphanol	0.7622
Codeine	734.2	Oxycodone	25.87	Levorphanol	0.4194
Meperidine	450.1	Diphenoxylate	12.37	Oxymorphone	0.4055
Propoxyphene	120.2	Alfentanil	7.391	Hydromorphone	0.3654
Pentazocine	117.8	Methadone	3.378	Buprenorphine	0.2157
		Nalbuphine	2.118	Sufentanil	0.1380
		Fentanyl	1.346		
		Morphine	1.168		

INDUCTION

Withdrawal can be precipitated by 1.5-2 mg dose

Rapid induction

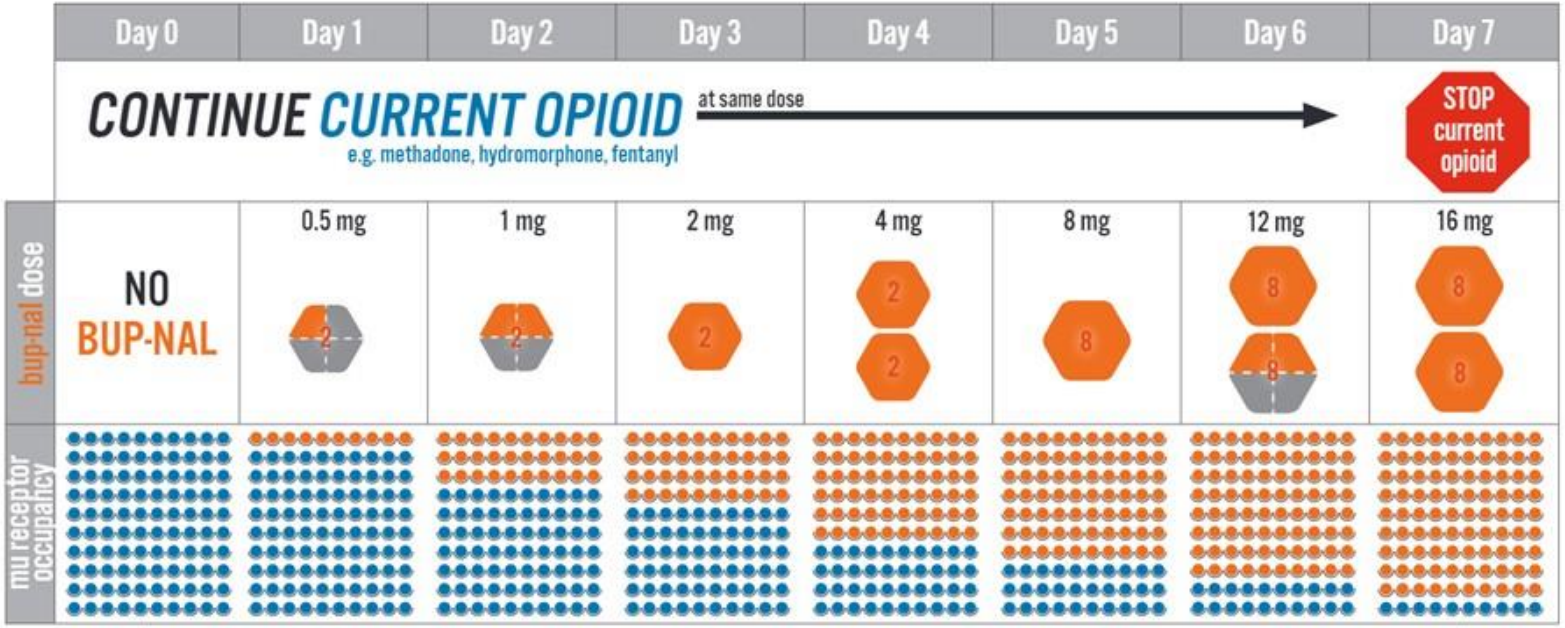
- Requires mild-moderate opioid withdrawal
- Full mu-opioid agonists must be stopped ahead of time
- Short-acting, 8-24 hours since last dose
- Long-acting, 24-72 hours since last dose

Bernese, gradual induction

- Continue full mu-opioid agonists throughout induction and discontinue at the end
- Increase the dose of Suboxone incrementally each day

Microdosing Initiation of Buprenorphine-Naloxone (SUBOXONE)

Microdosing (a.k.a. Bernese Method) is the process of slowly and gradually introducing buprenorphine-naloxone (bup-nal) into the body when someone is currently using another opioid (e.g. methadone, hydromorphone, fentanyl). This is done to prevent precipitated withdrawal, which is the sudden onset of withdrawal symptoms that occurs when the first dose of bup-nal is taken when other opioids are still in the body.



Microdosing initiation is considered off-label. Regimens can vary in length (usually 3-14 days) and bup-nal is usually given once or twice daily.

Rx FILES

Support for this infographic was provided by: Saskatchewan Health Authority

BERNESE METHOD INDUCTION

Day #	Suboxone schedule	Suboxone film size	Suboxone total daily dose	Receptors occupied by Suboxone	Full mu-opioid agonists
Day 0	No Suboxone	No Suboxone	0 mg	0%	Continue full mu-opioid agonists at the original dose
Day 1	0.5 mg SL	1/4 film (2-0.5 mg)	0.5 mg	10%	
Day 2	0.5 mg SL BID	1/4 film (2-0.5 mg)	1 mg	30%	
Day 3	1 mg SL BID	1/2 film (2-0.5 mg)	2 mg	40%	
Day 4	2 mg SL BID	Full film (2-0.5 mg)	4 mg	60%	
Day 5	2 mg SL TID	Full film (2-0.5 mg)	6 mg	65%	
Day 6	4 mg SL TID	Full film (4-1 mg)	12 mg	80%	
Day 7 & on	4 mg SL QID	Full film (4-1 mg)	16 mg	85%	Stop full mu-opioid agonists
Optional titration	8 mg SL TID or QID	Full film (8-2 mg)	24-32 mg	90-95%	

SUBOXONE SIDE EFFECTS

- Unpleasant orange flavor and aftertaste
  - Try citrus flavors afterwards
- Nausea
  - Typically improves in 1 week
  - May recur with uptitration
- Constipation
- Edema
- Sweating
- Rarely, reduced libido and/or altered menstruation
  - Seen less than with full mu-agonists

COMPLICATIONS

Breakthrough pain or Crisis

- Continue the maintenance dose of Suboxone* & add full mu-opioid agonists
- Outpatient, add hydromorphone
- Inpatient, add fentanyl ± ketamine/lidocaine

Overdose

- Due to mixed respiratory depressants
- Intravenous naloxone 0.5 mg/kg in a single dose
- (A typical dose of naloxone IV is 0.2 mg)

DEPRESCRIBING

Daily dose reduction over 7 days

STIGMA

- Counseling
- Patience
- Repeat

REFERENCES

- Daitch D, Daitch J, Novinson D, Frey M, Mitnick C, Pergolizzi J Jr. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. Pain Med. 2014 Dec;15(12):2087-94. doi: 10.1111/pme.12520. Epub 2014 Sep 12. PMID: 25220043.
- Daitch J, Frey ME, Silver D, Mitnick C, Daitch D, Pergolizzi J Jr. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. Pain Physician. 2012 Jul;15(3 Suppl):ES59-66. PMID: 22786462.
- Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. Drug Alcohol Depend. 2003 May 21;70(2 Suppl):S59-77. doi: 10.1016/s0376-8716(03)00060-7. PMID: 12738351.
- Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther. 2005 Sep-Oct;12(5):379-84. doi: 10.1097/01.mjt.0000160935.62883.ff. PMID: 16148422.
- Microdosing Initiation of Buprenorphine-Naloxone (Suboxone) [Internet]. Saskatoon, Saskatchewan, Canada: University of Saskatchewan, Pharmacy and Nutrition, RxFiles: Objective Comparisons for Optimal Drug Therapy; cited 2021 Nov 3. Available from: https://www.rxfiles.ca/RxFiles/uploads/documents/members/bup-nal-microdosing.pdf
- Nasser AF, Heidbreder C, Liu Y, Fudala PJ. Pharmacokinetics of Sublingual Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in Hepatitis C Virus-Seropositive Subjects, and in Healthy Volunteers. Clin Pharmacokinet. 2015 Aug;54(8):837-49. doi: 10.1007/s40262-015-0238-6. PMID: 25603822.
- Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011 Apr;59(3):385-90. doi: 10.1016/j.yrtph.2010.12.007. Epub 2011 Jan 6. PMID: 21215785.
- Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, Emerick T, Dopp A, Chhay S, Viscusi E. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021 Oct;46(10):840-859. doi: 10.1136/rapm-2021-103007. Epub 2021 Aug 12. PMID: 34385292.