Buprenorphine (Bup) Hospital Quick Start

- Any prescriber can order Bup in the hospital, even without an x-waiver.
- Bup is a high-affinity, partial agonist opioid that is safe and highly effective for treating opioid use disorder.
- If patient is stable on methadone or prefers methadone, recommend continuation of methadone as first-line treatment.

Uncomplicated* opioid withdrawal?**

NO → **Start Bup after withdrawal**
Supportive meds prn, stop other opioids

YES (stop other opioids)

Administer 8mg Bup SL

Withdrawal symptoms improved?

NO → **No Improvement**

Differential Diagnosis:

- **Withdrawal mimic:** Influenza, DKA, sepsis, thyrotoxicosis, etc. Treat underlyling illness.
- **Incompletely treated withdrawal:** Occurs with lower starting doses; improves with more Bup.
- **Bup side-effect:** Nausea, headache, dysphoria. Continue Bup, treat symptoms with supportive medications.
- **Precipitated withdrawal:** Too large a dose started too soon after opioid agonist.

  Usually time limited, self resolving with supportive medications.

  In complex or severe cases of precipitated withdrawal, OK to stop Bup and give short acting full agonists.

YES

Administer 2nd dose

Inpatient: 8mg. Subsequent days, titrate from 16mg with additional 4-8mg prn cravings.
ED: 8-24mg. Consider discharge with higher loading dose.

Maintenance Treatment 16 mg Bup SL/day

Titrate to suppress cravings;
Usual total dose 16-32mg/day

Discharge

- Document Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.
- **If no X-waiver:** Use loading dose up to 32mg for long effect and give rapid follow up.
- **If X-waiver:** Check CURES (not required in Emergency Department if ≤7 day prescription), prescribe sufficient Bup/Nx until follow-up.

Overdose Education Naloxone Kit

Naloxone 4mg/0.1ml intranasal spray

Buprenorphine Dosing

- Either Bup or Bup/Nx (buprenorphine/naloxone) films or tab sublingual (SL) are OK.
- If unable to take oral/SL, try Bup 0.3mg IV/IM.
- OK to start with lower initial dose: Bup 2-4mg SL.
- Total initial daily dose above 16mg may increase duration of action beyond 24 hrs.
- Bup SL onset 15 min, peak 1 hr, steady state 7 days
- May dose qday or if co-exisiting chronic pain split dosing TID/QID.

*Complicating Factors

- Altered mental status, delirium, intoxication
- Severe acute pain, trauma or planned large surgeries
- Organ failure or other severe medical illness
- Recent methadone use

**Diagnosing Opioid Withdrawal

Subjective symptoms AND one objective sign

Subjective: Patient reports feeling "bad" due to withdrawal (nausea, stomach cramps, body aches, restlessness, hot and cold, stuffy nose)

Objective: ***[at least one]*** restlessness, sweating, rhinorrhea, dilated pupils, watery eyes, tachycardia, yawning, goose bumps, vomiting, diarrhea, tremor

Typical withdrawal onset:
≥ 12 hrs after short acting opioid
≥ 24 hrs after long acting opioid
≥ 48 hrs after methadone (can be >72 hrs)

If unsure, use COWS (clinical opioid withdrawal scale). Start if COWS ≥ 8 AND one objective sign.

If Completed Withdrawal:
Typically >72 hrs since last short-acting opioid, may be longer for methadone. Start Bup 4mg q4h prn cravings, usual dose 16-32mg/day. Subsequent days, OK to decrease frequency to qday

Opioid Analgesics

- Pause opioid pain relievers when starting Bup.
- OK to introduce opioid pain relievers after Bup is started for breakthrough pain. Do not use methadone with Bup.

Supportive Medications

- Can be used as needed while waiting for withdrawal or during induction process.

Pregnancy

- Bup monoproduct or Bup/Nx OK in pregnancy.
- Consider referencing buprenorphine in pregnancy guide.

SEPTEMBER 2020

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

REFERENCES

Buprenorphine (Bup) Hospital Quick Start

AUTHORS

James Gasper Pharm D, Kristin Harter PharmD, Andrew Herring MD, David Kan MD, Sky Lee MD, Walter Ling MD, Josh Luftig PA, Aimee Moulin MD, Arianna Sampson PA, Hannah Snyder MD, Rebecca Trotzky-Sirr MD

REFERENCES

Ahmadi J, Jahromi MS, Ghahremani D, London ED. Single high-dose buprenorphine for opioid craving during withdrawal. Trials. 2018 Dec 10;19: 675. doi: 10.1186/s13063-018-3055-z

Ang-Lee K, Oreskovich MR, Saxon AJ, et al. Single dose of 24 milligrams of buprenorphine for heroin detoxification: an open-label study of 5 inpatients. J Psychoactive Drugs. 2006 Dec;38(4): 505-512. doi: 10.1080/02791072.2006.10400589

Bhatraju EP, Grossman E, Tofighi B, et al. Public sector low threshold office-based buprenorphine treatment: outcomes at year 7. Addict Sci Clin Pract. 2017;12: 7. doi:10.1186/s13722-017-0072-2

D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015 Apr 28;313(16): 1636–1644. doi:10.1001/jama.2015.3474

Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and μ-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend. 2014 Nov 1;0: 1–11. doi:10.1016/j.drugalcdep.2014.07.035

Herring AA, Perrone J, Nelson LS. Managing opioid withdrawal in the emergency department with buprenorphine. Ann Emerg Med. 2019;73(5): 481-487. doi: 10.1016/j.annemergmeed.2018.11.032

Hopper JA, Wu J, Martus W, Pierre JD. A randomized trial of one-day vs three-day buprenorphine inpatient detoxification protocols for heroin dependence. J Opioid Manag. 2005 Mar-Apr;1(1): 31-35. doi: 10.5055/jom.2005.0009

Kutz I, Reznik V. Rapid heroin detoxification using a single high dose of buprenorphine. J Psychoactive Drugs. 2001 Apr-Jun;33(2): 191-193. doi: 10.1080/02791072.2001.10400484

Jacobs P, Ang A, Hillhouse MP, et al. Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories. Am J Addict. 2015 Oct;24(7): 667–675. doi:10.1111/ajad.12288

Jones HE, Johnson RE, Lorraine Milio. Post-cesarean pain management of patients maintained on methadone or buprenorphine. Am J Addict. 2006 May-Jun;15(3)258-259. doi: 10.1080/10550490600626721

Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014 Aug;174(8): 1369–1376. doi:10.1001/jamainternmed.2014.2556

Committee opinion no. 711 summary: Opioid use and opioid use disorder in pregnancy. Obstet Gynecol. 2017;130(2):488-489. doi:10.1097/AOG.0000000000002229

Meyer M, Wagner K, Benvenuto A, Plante D, Howard D. Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. Obstet Gynecol. 2007 Aug;110(2 Pt 1):261-266. https://doi.org/10.1097/01.AOG.0000275288.47258.e0

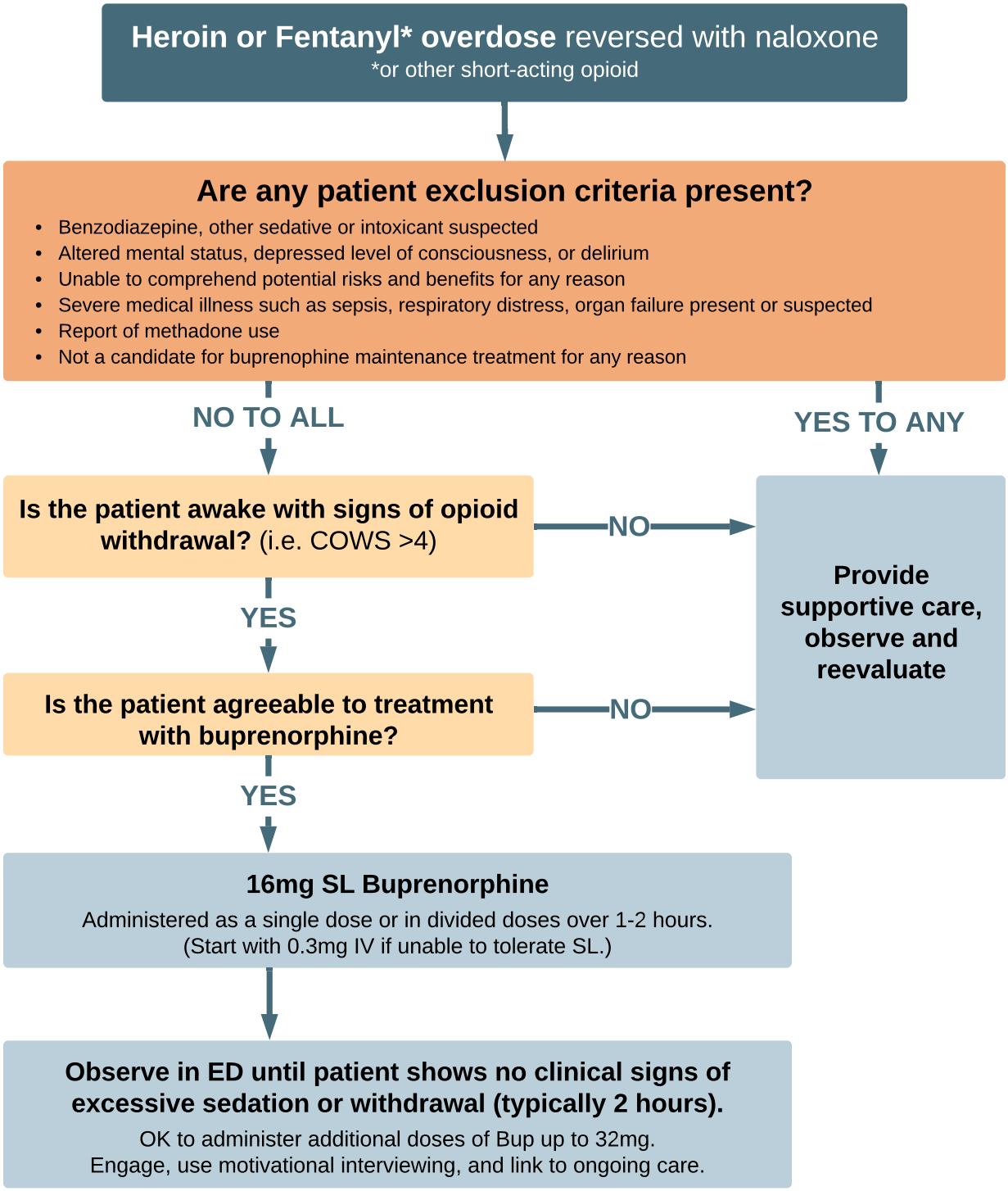
Oreskovic MR, Saxon AJ, Ellis MLK, Malte CA, Roux JP, Knox PC. A double-blind, double-dummy, randomized, prospective pilot study of the partial mu opiate agonist, buprenorphine, for acute detoxification from heroin. Drug Alcohol Depend. 2005 Jan 7;77(1): 71-79. doi: 10.1016/j.drugalcdep.2004.07.008

Walsh SL, Eissenberg, T. The clinical pharmacology of buprenorphine: Extrapolating from the laboratory to the clinic. Drug and Alcohol Depend. 2003 May 21;70(2 Suppl): S13-27. doi: 10.1016/s0376-8716(03)00056-5

Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994 May;55(5): 569-580. doi: 10.1038/clpt.1994.71

Starting Buprenorphine Immediately after Reversal of Opioid Overdose with Naloxone

Based on Herring, A. A., Schultz, C. W., Yang, E., & Greenwald, M. (2019). Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *The American journal of emergency medicine*.



NOVEMBER 2019

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

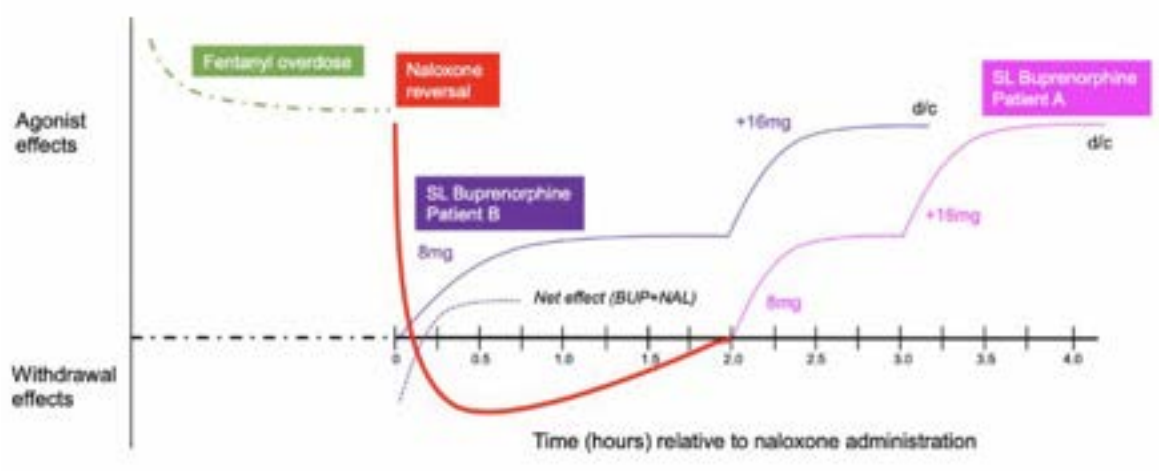
UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

Buprenorphine After Opioid Overdose (ODNaloxoneBup)

The minimum inclusion criteria for ODNaloxoneBup is an otherwise healthy patient with no suspected co-ingestions and no recent methadone use with a normal level of consciousness, normal mental status, and the ability to provide informed consent. Administration of buprenorphine (Bup) to patients intoxicated with alcohol, benzodiazepines or other sedative can result in potentially dangerous respiratory depression. Patients with acute illness or severe chronic illness such as infection, heart failure, liver failure, respiratory failure or acute renal failure can experience unpredictable sedation and respiratory depression. Patients with altered mental status are not able to provide a reliable history or adequately consider the risks and benefits to provide informed consent. Patients taking methadone should be supported to continue methadone treatment; overdose is not an indication to switch to buprenorphine and may disrupt care. Additionally, the interaction with buprenorphine and methadone is not well understood and potentially adverse antagonistic (withdrawal) interactions can occur.

Be prepared There are two "worst case scenario" adverse events possible with ODNaloxoneBup: 1) additive sedation with respiratory depression and 2) precipitated withdrawal. While neither of these has been reported at this time, any ED should be prepared and willing to adequately manage these potential complications. Reversal of buprenorphine is accomplished with high-dose naloxone (2-3mg IV push followed by 4mg/hr infusion) (9,10). Precipitated withdrawal is treated with empirically titrated with a multimodal approach that may include: benzodiazepines, alpha-2 agonists (clonidine, dexmedetomidine, lofexidine), high affinity full agonist opioids (hydromorphone), ketamine, and dopamine antagonists (e.g. metoclopramide or haldoperidol).

Why this works Once naloxone has reversed opioid overdose (regardless of whether withdrawal signs/symptoms have been precipitated), initiation of buprenorphine should yield a relative increase in mu-opioid receptor (MOR) agonism and be experienced as stabilization or withdrawal relief. *In vitro (+NaCl)*, naloxone exhibits 5-fold higher MOR affinity than morphine and comparable MOR affinity as sufentanil and, under these same physiological conditions, buprenorphine exhibits 6-fold higher MOR affinity than naloxone. Following naloxone displacement and reversal of opioid overdose, buprenorphine is therefore expected to displace naloxone from available MORs (and residual naloxone effect should wash out rapidly due to its pharmacokinetics; (see figure below). Once bound to MORs, buprenorphine's high-affinity, longer-acting MOR occupancy should effectively prevent return of full agonist toxicity (provide opioid blockade) even if relatively high concentrations of full agonist remain in the circulation. The positive treatment responses we have observed suggest the possibility that as naloxone is metabolized and/or displaced from MORs a mixed state of buprenorphine partial agonism and full opioid agonism (from the residual opioid that caused the overdose) occur, thereby avoiding an abrupt transition from full to partial agonism that would have been experienced as precipitated withdrawal.



References:

Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. 2014;144.

Boysen K, Hertel S, Chraemmer-Jørgensen B, Risbo A, Poulsen NJ. Buprenorphine antagonism of ventilatory depression following fentanyl anaesthesia. Acta Anaesthesiol Scand. 1988 Aug;32(6):490–2.

Van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 2006 Jul;105(1):51–57.

Rzasa Lynn R, Galinkin J. Naloxone dosage for opioid reversal: current evidence and clinical implications. Ther Adv Drug Saf. 2018 Jan;9(1):63–88.

Ahmed N, Horlacher R, Fudin J. Opioid Withdrawal: A New Look At Medication Options. Practical Pain Management [Internet]. 2015 Nov [cited 2019 Apr 12];15(9). Available from: https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/opioid-withdrawal-new-look-medication-options

Clark MJ, Carter BD, Medzihradsky F. Selectivity of ligand binding to opioid receptors in brain membranes from the rat, monkey and guinea pig. Eur J Pharmacol. 1988 Apr 13;148(3):343–51.

Müller H, Gerlach H, Gips H, Richter M, Börner U, Hempelmann G. [Intra- and postoperative interactions between the 2 opioids fentanyl and buprenorphine]. Anaesthesist. 1986 Apr;35(4):219–25.

Tröster A, Ihmsen H, Singler B, Filitz J, Koppert W. Interaction of fentanyl and buprenorphine in an experimental model of pain and central sensitization in human volunteers. Clin J Pain. 2012 Oct;28(8):705–11.

Volpe DA, Tobin GAM, Mellon RD, Katki AG, Parker RJ, Colatsky T, et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology. 2011 Apr 1;59(3):385–90.