Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine
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Buprenorphine for Medication-Assisted Therapy (MAT) in the Emergency Department

Introduction

1. Between 1999-2017, ~400,000 people died from opioid overdose, which tops that of deaths from HIV in the same time period.
2. Recently, treatment options for opioid use disorder (OUD) in the emergency department (ED) has been a common debate with various therapeutic regimens proposed
3. Buprenorphine has emerged as a common treatment modality for MAT with many caveats to its use in the ED

Pharmacology

	Buprenorphine ± Naloxone
Dose	• **Day 1**: 2-4 mg may titrate dose, based on control of acute withdrawal symptoms every 2 hours up to a **total dose of buprenorphine 8 mg/naloxone 2 mg** • **Day 2:** Previous dose from day 1 if no withdrawal symptoms present; if symptoms of withdrawal present, increase day 1 dose by 4 mg. If withdrawal symptoms not relieved after >2 hours, may administer 4 mg; **maximum daily dose on day 2: 16 mg daily.**
Administration	• **Sublingual film:** o **Administer film whole; do not cut, chew, or swallow**. Place one film under the tongue until the film completely dissolves, close to the base on the left or right side. If more than one film is needed, the additional film should be placed under the tongue on the opposite side from the first film.
Formulations	**Buprenorphine+ Naloxone Sublingual/Buccal Films:** • Generic Buprenorphine HCl-Naloxone HCl Sublingual, Bunavail Buccal, and Suboxone Sublingual **Buprenorphine:** • Sublingual: Subutex and generic buprenorphine HCL • Injection: Buprenex and generic buprenorphine HCL
PK/PD	**Absorption** • **Bioavailability- IM: ~95% ; SL: 31%** • Liquids reduces absoption 23% to 27% **Distribution** • Vd: 97 to 187 L (adults) • **Time to Peak Concentration- SL: 1.5-4 hours** **Metabolism** • Hepatic: **Extensive via CYP3A4;** • Metabolites: Norbuprenorphine: Active **Elimination** • Fecal: 69% • **Renal: 30%**
Adverse Effects	• QT prolonging (less than methadone) • precipitate withdrawal in presence of opioids/opiates • Tachycardia, restlessness and agitation, nausea and vomiting
Drug Interactions and warnings	• QT prolonging medications such as fluoroquinolones (moxifloxacin), macrolides, antipsychotics, tricyclic antidepressants (TCAs) • Strong CYP450 3A4 inhibitors: statins, amiodarone, haloperidol, macrolides, azole antifungals (fluconazole, ketoconazole), calcium channel blockers, grapefruit juice

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How Does Buprenorphine Works?

- Buprenorphine is a partial agonist of mu-opioid receptors as well as a weak antagonist at the kappa receptors
  - Has higher affinity to the Mu receptor (**only child syndrome and wants all of mama Mu and not too much of daddy Kappa's attention**)
  - Partial agonism ="**Ceiling Effect**" (All bark and no bite)
  - **Slow dissociation** (Doesn't know when to move on from his ex Kappmuphenia)

Induction Therapy in the ED

When to initiate?	• Last dose of opioid/opiate ≥ 6-24 hours • Moderate withdrawal (COWS ≥ 6-8)
First dose of sublingual (SL) buprenorphine	• 2-8 mg then reassess in 1-2 h
If symptoms NOT controlled after first dose	• Titrate by 2-4 mg based on Clinical Opioid Withdrawal Symptoms (COWS)
Max dose of SL Buprenorphine	• Day 1: 8 mg total dose • Day 2: 16 mg as single dose

Buprenorphine Prescription Requires an X-Wavier Provider

- According to the Drug Addiction Treatment Act of 2000 (DATA 2000), to qualify to prescribe buprenorphine, physicians (also NPs, PAs) must complete an 8-hour course and complete an application to obtain a waiver (DEAX waiver).
  - https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/buprenorphine-physician-training
- However, according to DEA, a non X-waiver provider can prescribe buprenorphine if:
  - Not more than one day's medication may be administered or given to a patient at one time
  - Treatment may not be carried out for more than 72 hours
  - The 72-hour period cannot be renewed or extended

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Srivastava, 2019	RCT N=26	• Buprenorphine • Clonidine	Buprenorphine group were **more likely to be receiving opioid agonist treatment at the 1-month mark** compared with those participants who received clonidine to treat their withdrawal (P = .011)
Larochelle, 2018	Observational N=17,568	• Methadone maintenance treatment (MMT) • Buprenorphine • Naltrexone	As compared to naltrexone, buprenorphine treated patient was associated with **decreases in both all-cause mortality** (adjusted HR, 0.63) and **opioid-related mortality (HR, 0.62]).**
D'Onofrio, 2017	Observational N=290	• ED-initiated buprenorphine	ED-initiated buprenorphine **was associated with ↑ engagement in outpatient opioid addiction treatment programs + ↓ illicit opioid use**
Gowing, 2017	Cochrane review N= 3048 participants	• Buprenorphine • Naltrexone • Clonidine • Methadone	Buprenorphine is **more effective than clonidine for managing opioid withdrawal** in terms of severity of withdrawal, duration of withdrawal treatment, and the likelihood of treatment completion
Berg, 2007	Observational N=11,019	• Buprenorphine • Symptomatic treatment • Placebo	Subjects who received buprenorphine were **less likely to return to the same ED within 30 days for a drug-related visit (8%)** compared to those who received symptomatic treatment (17%) (p<0.05).

References

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