The Utility of Treating Opioid Use Disorder with Buprenorphine-Naloxone in the Intensive Care Setting

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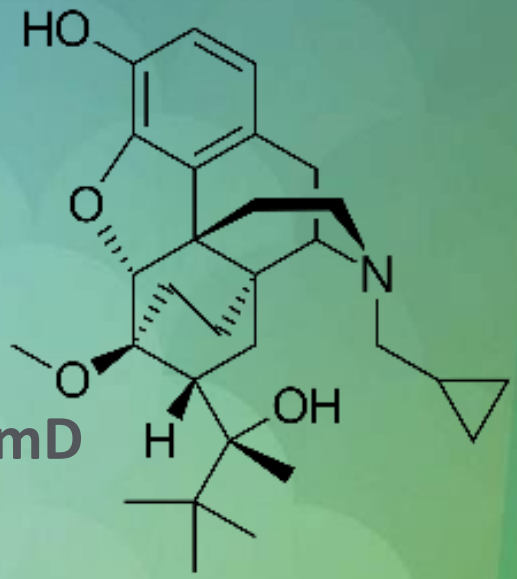

Additional Slide Credit: Abbigail Collins, PharmD

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Conflict of Interest Statement

The authors of this presentation have no financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

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Abbreviations

- ACOG – American College of Obstetricians and Gynecologists
- AHRF – Acute Hypoxic Respiratory Failure
- ASAM – American Society of Addiction Medicine
- BID – Twice Daily
- BUP – Buprenorphine
- COWS – Clinical Opiate Withdrawal Scale
- CYP – Cytochrome P450
- DATA – Drug Addiction Treatment Act
- DDI – Drug-Drug Interactions
- DSM5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
- FDA – U.S. Food and Drug Administration
- KAR – Kentucky Administrative Regulations
- LFT – Liver Function Test
- ICU – Intensive Care Unit
- IVDU – Intravenous Drug Use
- MME – Morphine Milligram Equivalents
- MOA – Mechanism of Action
- MOR – Mu Opioid Receptor
- MOUD – Medication for Opioid Use Disorder
- MV – Mechanical Ventilation
- OUD – Opioid Use Disorder
- SAMHSA – Substance Abuse and Mental Health Services Administration
- SL – Sublingual
- TID – Three Times Daily
- ULN – Upper Limit of Normal

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Objectives:

- Review the mechanism of action of transmucosal buprenorphine-naloxone versus full μ-opioid agonists
- Discuss the rationale for allowing concomitant use of partial and full μ-opioid receptor agonists
- Differentiate between a traditional induction and a rapid induction of transmucosal buprenorphine and understand the utility of each
- Design appropriate transmucosal buprenorphine regimens based on patient-specific factors

Epidemiology

- In 2020, 2.7 million Americans had an Opioid Use Disorder
- Opioid overdoses accounted for 68,000 deaths in the US in 2020
- Kentucky is continually among the top ten states for opioid-related deaths
- In 2020, over 1,900 Kentuckians died from drug overdoses, of which 90% involved opioids

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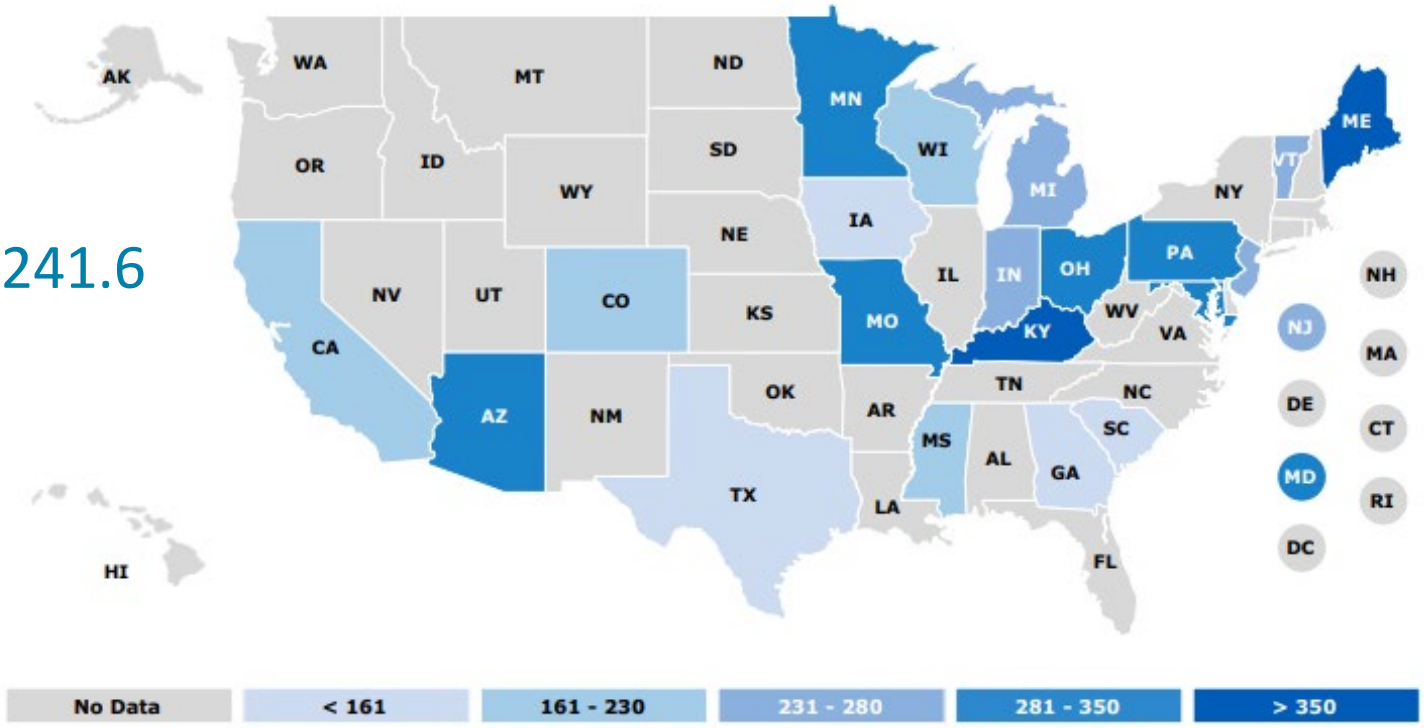
National Institute on Drug Abuse (NIH) | Centers for Disease Control

Rate of Opioid Inpatient Stays

National Rate: 241.6

KY Rate: 407.4

Rate of Opioid Inpatient Stays (per 100,000 people)



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HCUP Fast Stats. Healthcare Cost and Utilization Project (HCUP). September 2021. Agency for Healthcare Research and Quality, Rockville, MD. https://datatools.ahrq.gov/hcup-fast-stats

OUD Diagnostic Criteria

- *Defined as a problematic pattern of opioid use that causes clinically significant impairment or distress*

2-3 = mild disorder

4-5 = moderate disorder

≥ 6 = severe disorder

DSM-5 diagnostic criteria for OUD

Patients must meet 2 of the following 11 criteria to receive a diagnosis of OUD:

1. Opioids are often taken in larger amounts or longer period than intended
2. Unsuccessful efforts to control opioid use
3. Large segment of time allocated to obtaining, using, or recovering from opioids
4. Strong desire to use opioids
5. Use of opioids is deterring one from daily activities such as work, school, or home
6. Continued opioid use despite its use causing an inability to fulfill responsibilities
7. Reduction or elimination of social occupational or recreational activities due to opioid use
8. Ongoing opioid use although physically hazardous
9. Ongoing opioid use despite having knowledge of such hazards
10. Experiencing tolerance to opioids
11. Experiencing withdrawal from opioids

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De Nadai AS, et al. J Consult Clin Psychol. 2019;87(10):849-858.

Impact on ICU Care

- This patient population requires higher levels of opioids to maintain sedation goals
    - 2007 retrospective cohort study found that SUD patients also have a larger fluctuation in sedation levels
- Spontaneous awakening trials often induce withdrawal in opioid-dependent patients, resulting in increased agitation
- Severe agitation is associated with longer ICU LOS, duration of MV, and self-extubation

- Starting MOUD in the ICU setting prevents delay in care and treats the underlying disease

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Wit, et al. BMC Anesthesiol. 2007 Mar 14;7:3.
Woods, et al. Intensive Care Med. 2004 Jun;30(6):1066-72.

ASAM OUD Treatment Guidelines

- The use of methadone or buprenorphine is recommended for opioid withdrawal over abrupt cessation
- Abrupt cessation results in increased risk of relapse, overdose, and death
- Symptomatic management alone is not recommended

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J Addict Med. Mar/Apr 2020;14(2S Suppl 1):1-91.

Opioid Withdrawal

Clinical Opiate Withdrawal Scale (COWS): *Provides an assessment of withdrawal and severity*

Clinical Opiate Withdrawal Scale (COWS)

For each item, circle 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 and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate:_____beats/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

GI Upset: *over last ½ hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 Multiple episodes of diarrhea or vomiting

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

Tremor *observation of outstretched hands*
0 No tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness *Observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 Unable to sit still for more than a few seconds

Yawning *Observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/ muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Runny nose or tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

Total Score _____
The total score is the sum of all 11 items

Initials of person completing Assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal
Source: Wesson and Ling 2003[STN]

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Opioid Receptors and Functions

- Mu (μ):
  - Analgesia
  - Sedation, vomiting, respiratory depression, pruritus, physical dependence, euphoria
- Delta (δ):
  - Analgesia, spinal analgesia
- Kappa (κ):
  - Analgesia
  - Sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria

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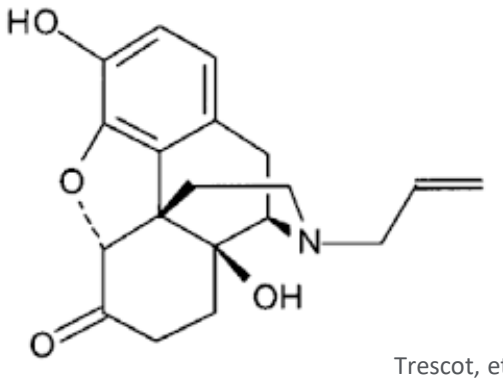
Trescot, et al. Pain Physician. 2008 Mar;11(2 Suppl):S133-53.

Buprenorphine MOA

- Semisynthetic opioid: partial μ-opioid receptor agonist and κ-opioid receptor antagonist
  - In the absence of agonists, relieves withdrawal and reduces cravings
- High binding affinity for μ-opioid receptor
  - In the presence of agonists, competitively binds and act as an antagonist
- Partial agonism has a ceiling effect on:
  - Respiratory depression, euphoria, physiologic dependence



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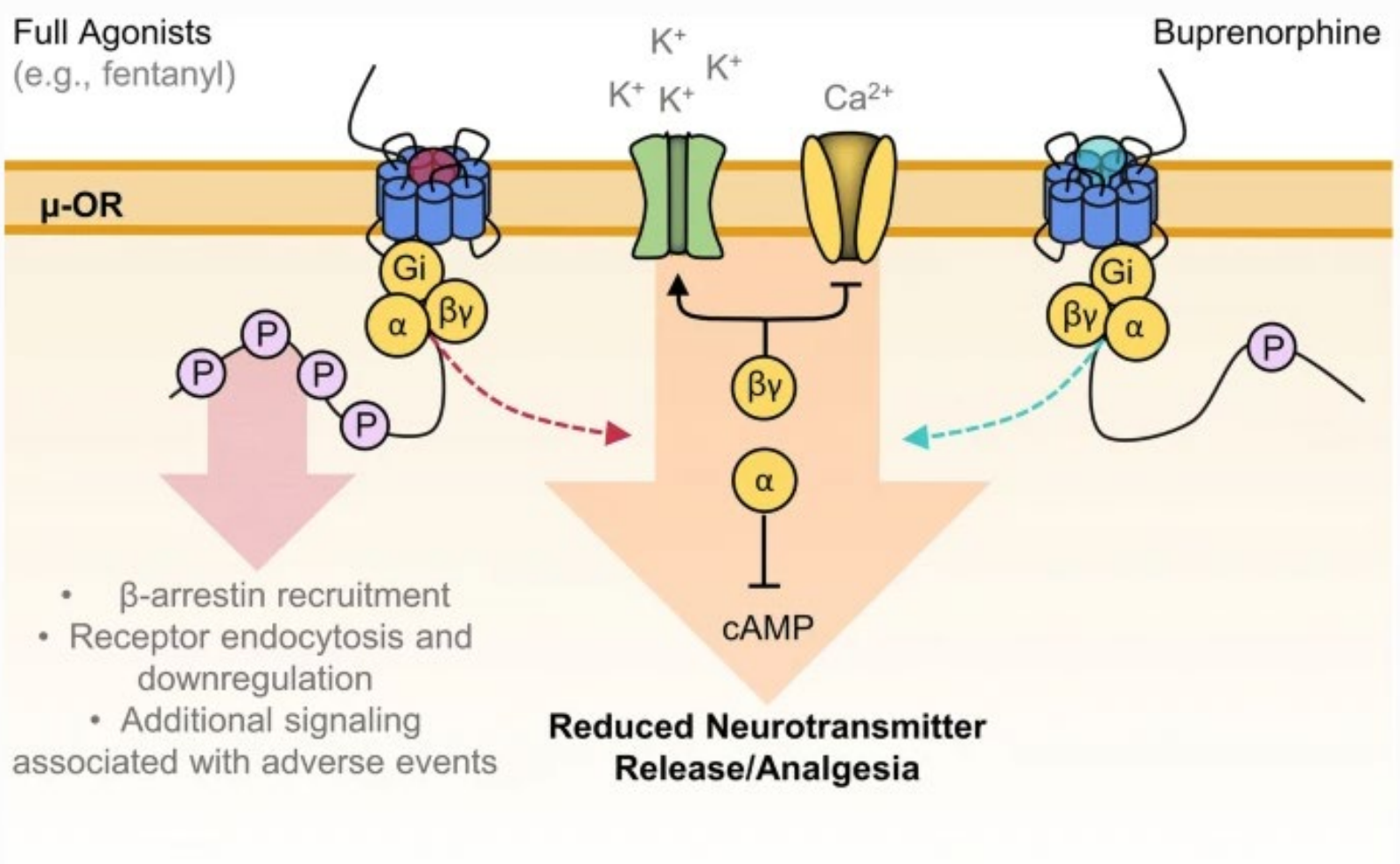

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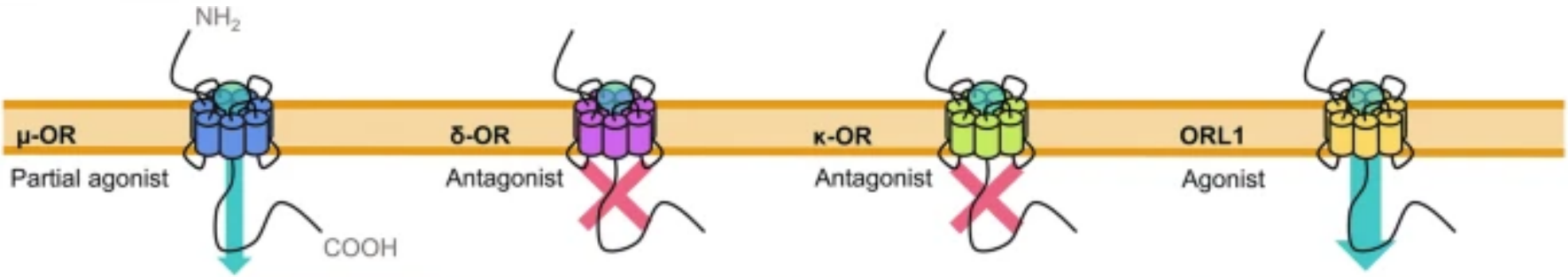
Gudin, et al. Pain Ther. 2020 Jun;9(1):41-54.

Buprenorphine Actions



- Potent analgesia
- Ceiling on respiratory depression and euphoria
- Limited impact on GI motility
- Limited physical dependence, abuse potential, and withdrawal symptoms
- Reduced immunosuppression and impact on the HPA axis
- Reduction in suicidal thoughts, anxiety, and depression
- Limited dysphoria

- Anti-opioid effects
- Myocardial protection
- Limited impact on GI motility*
- Limited respiratory depression*

- Reduced depression, dysphoria, suicidal tendencies, anxiety, and hostility
- Limited potential for addiction* and tolerance
- Reduced immunosuppression

- Enhanced spinal analgesia
- Reduced supraspinal analgesia
- Diminished opioid-rewarding effects
- Limited potential for tolerance

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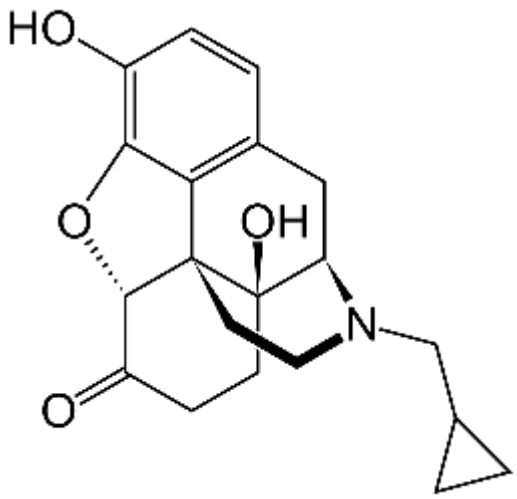
Gudin, et al. Pain Ther. 2020 Jun;9(1):41-54.

Naloxone

- MOA: a pure μ-opioid receptor antagonist
  - Competes and displaces opioids resulting in withdrawal
- Poor oral absorption – used to reduce misuse of buprenorphine
- Metabolism via hepatic glucuronidation



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Trescot, et al. Pain Physician. 2008 Mar;11(2 Suppl):S133-53.

Naloxone Considerations

- **LFT's > 5x ULN or Child-Pugh Class C:** avoid naloxone-containing transmucosal buprenorphine maintenance products

- **Pregnancy:** concentrations found in cord blood, but other studies have shown no adverse maternal or neonatal outcomes when using combination therapy during pregnancy
    - 2020 meta-analysis reviewing 5 studies found that women treated with combination therapy have similar outcomes

- ACOG recommends the use of mono-product BUP or naloxone containing BUP therapy for OUD treatment in pregnancy

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Wiegand et al. AJP Rep. 2016 Oct;6(4):e385-e390.
Link et al. Am J Obstet Gynecol MFM. 2020 Aug;2(3):100179
Obstet Gynecol. 2017 Aug;130(2):e81-e94.

Suboxone Traditional Induction

- Patient must show signs of withdrawal (COWS ≥ 7)
  - Typical wait of 12-16 hours since last opioid use
  - Wait not required if naloxone reversal was required for overdose
- Day 1: BUP 2-4 mg 1-time
  - Repeat COWS every 2-4 hours
  - May give an additional 1-time dose if COWS ≥ 7
- Day 2: day 1 total daily dose
  - Continue same titration scale
- Typical maintenance dose: 16 mg/day of buprenorphine component

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American Society of Addiction Medicine, 2020.

Precipitated Withdrawal

- Opioid dependent patient receives an agent that quickly reverses opioids
  - Partial Agonist: BUP
  - Antagonist: naloxone, naltrexone
- Symptoms are more severe than spontaneous withdrawal
- Methadone is a full μ-opioid receptor agonist and therefore will not cause precipitated withdrawal
- Historically, BUP therapy has been delayed to avoid this

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Rapid Micro-Induction

- Novel dosing protocol initiated while patient receives full agonist therapy
- Day 1: BUP 0.5 mg SL every 6 hours
  - Total Daily Dose: 2 mg
- Day 2: BUP 1 mg SL every 6 hours
  - Total Daily Dose: 4 mg
- Day 3: BUP 4 mg SL every 12 hours
  - Total Daily Dose: 8 mg
- Day 4: BUP 16 mg SL once daily
- Can also titrate to dose patient was maintained on outpatient

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Hamata, et al. J Addict Med. 2020 Dec;14(6):514-517

Rapid Micro-Induction

- Any patient continuing to receive opioids must use this dosing protocol to avoid precipitated withdrawal, regardless if BUP was a home medicine
- Beneficial for ICU patients that are unable to be weaned from opioids yet:
    - Recent surgery
    - Uncontrolled pain
    - Sedation for mechanical ventilation
- More tolerable for the patient in comparison to a traditional induction

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Literature Review

- 2016 Case Study *"Bernese Method" (n =2)*
  - First study to show induction can overlap with full μ-opioid agonists without causing withdrawal
  - Gradual titration from 0.2 mg daily over 10 days
- 2019 Case Study (n = 2)
  - Case 1: 0.25 mg every 4 hours titrated over 5 days
  - Case 2: 0.5 mg every 3 hours titrated over 3 days
- 2020 Case Study (n = 1)
  - Utilized a very similar titration as 2019 but in a critically-ill and intubated patient
  - Successfully titrated to maintenance dose and off of fentanyl

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Vogel, et al. Am J Med 2016 Jul 20;7:99-105.
Klaire, et al. Am J Addict. 2019 Jul;28(4):262-265
Hamata, et al. J Addict Med. 2020 Dec;14(6):514-517

Case Reports › J Addict Med. 2020 Dec;14(6):514-517. doi: 10.1097/ADM.0000000000000675.

Rapid Micro-induction of Buprenorphine/Naloxone for Opioid Use Disorder in a Critically ill Intubated Patient: A Case Report

Basia Hamata [1], Donald Griesdale, Jessica Hann, Pouya Rezazadeh-Azar

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Critically Ill Case Report

- 29 YOF presented with distributive shock, sepsis, & recurrent endocarditis. Intubated within 24 hours for AHRF secondary to bilateral septic emboli.
- MV Day 3: unable to tolerate fentanyl wean to 150 mcg/min
- MV Day 5: BUP started for ongoing withdrawal and escalating IV opioid doses

	Buprenorphine/Naloxone Dosing	Total Daily Dose	Fentanyl Infusion (mcg/hr)	Adjuvant Treatment
Day 0 (intubation day 4)	N/A		200 mcg/min	N/A
Day 1 (intubation day 5)	0.25 mg SL q 3 h	2 mg	200 mcg/min	Clonidine 0.1 mg q 8 h Gabapentin 100 mg q 8 h Methotrimeprazine 10 mg q 4 h
Day 2 (intubation day 6)	0.5 mg SL q 3 h	4 mg	200 mcg/min	Clonidine 0.1 mg q 8 h Gabapentin 100 mg q 8 h Methotrimeprazine 10 mg q 4 h
Day 3 (intubation day 7)	1.0 mg SL q 3 h	8 mg	200 mcg/min then fentanyl wean initiated†	Clonidine 0.1 mg q 8 h Gabapentin 100 mg q 8 h Methotrimeprazine 10 mg q 4 h
Day 4 (intubation day 8)	12 mg SL + 1 mg q 3 h prn for opioid w/d	19 mg	Fentanyl infusion stopped when full dose of 12 mg buprenorphine/naloxone administered	Clonidine 0.1 mg q 8 h Gabapentin 100 mg q 8 h Methotrimeprazine 10 mg q 4 h

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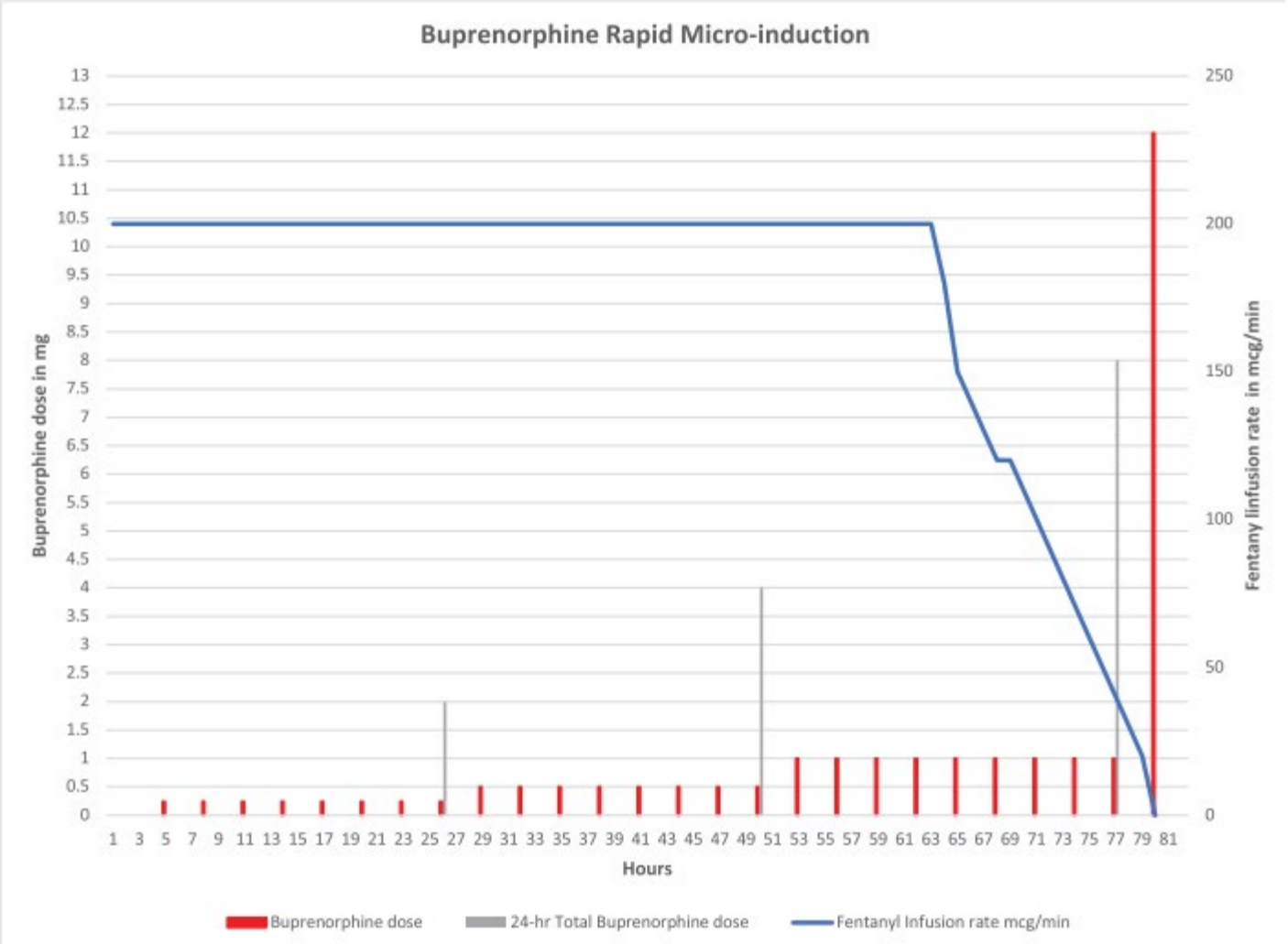
Hamata, et al. J Addict Med. 2020 Dec;14(6):514-517

Induction with Simultaneous Fentanyl Wean



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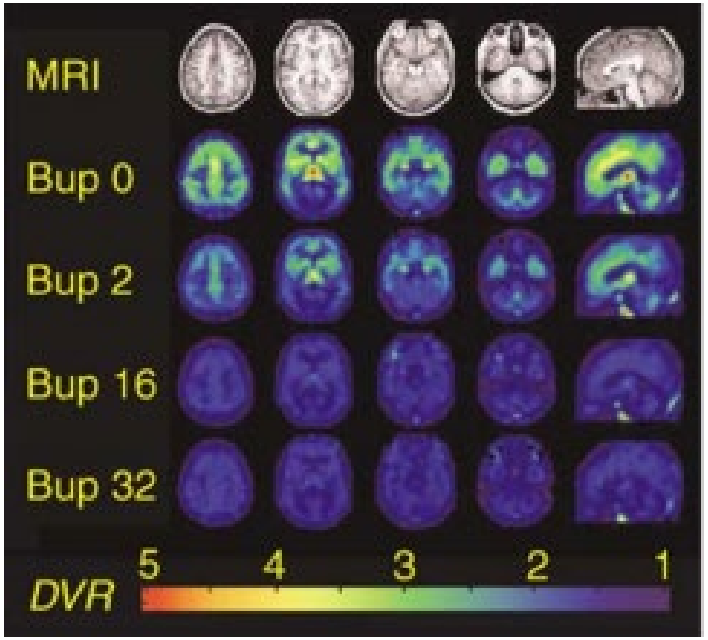
Hamata, et al. J Addict Med. 2020 Dec;14(6):514-517

Micro-Induction Mechanisms

- A 2003 study used PET and MRI imaging to confirm that higher doses of BUP decrease the # of MORs available for agonism
- BUP doses of 2, 16, and 32 mg/day reduced MOR binding availability by 41%, 80%, and 84%
- With “micro” doses of 0.25-1 mg/day, little is being displaced



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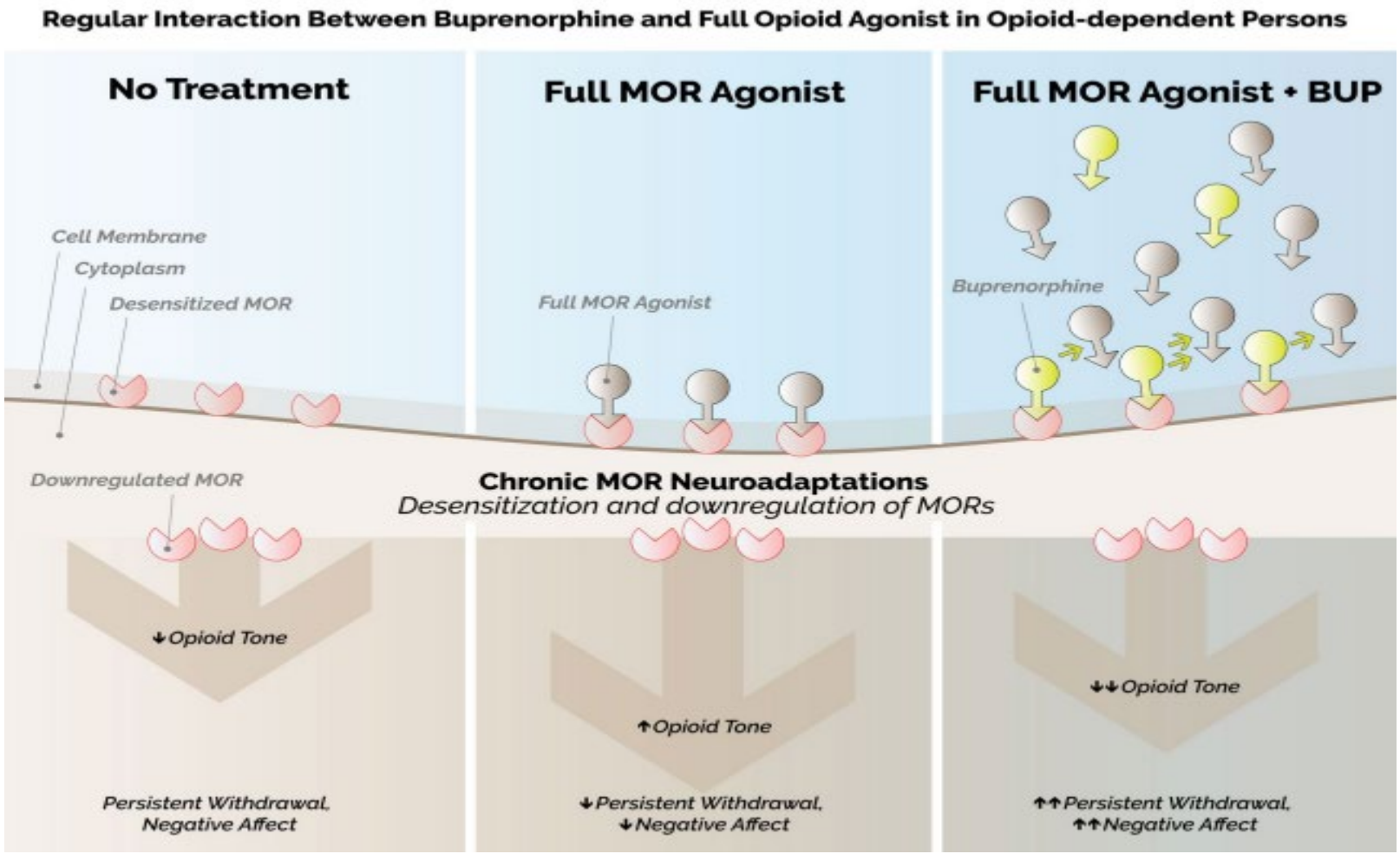
Greenwald MK, et al. Neuropsychopharmacology. 2003 Nov;28(11):2000-9.
De Aquino JP et al. Clin Drug Investig. 2021 May;41(5):425-436.

MOR Signaling Adaptations



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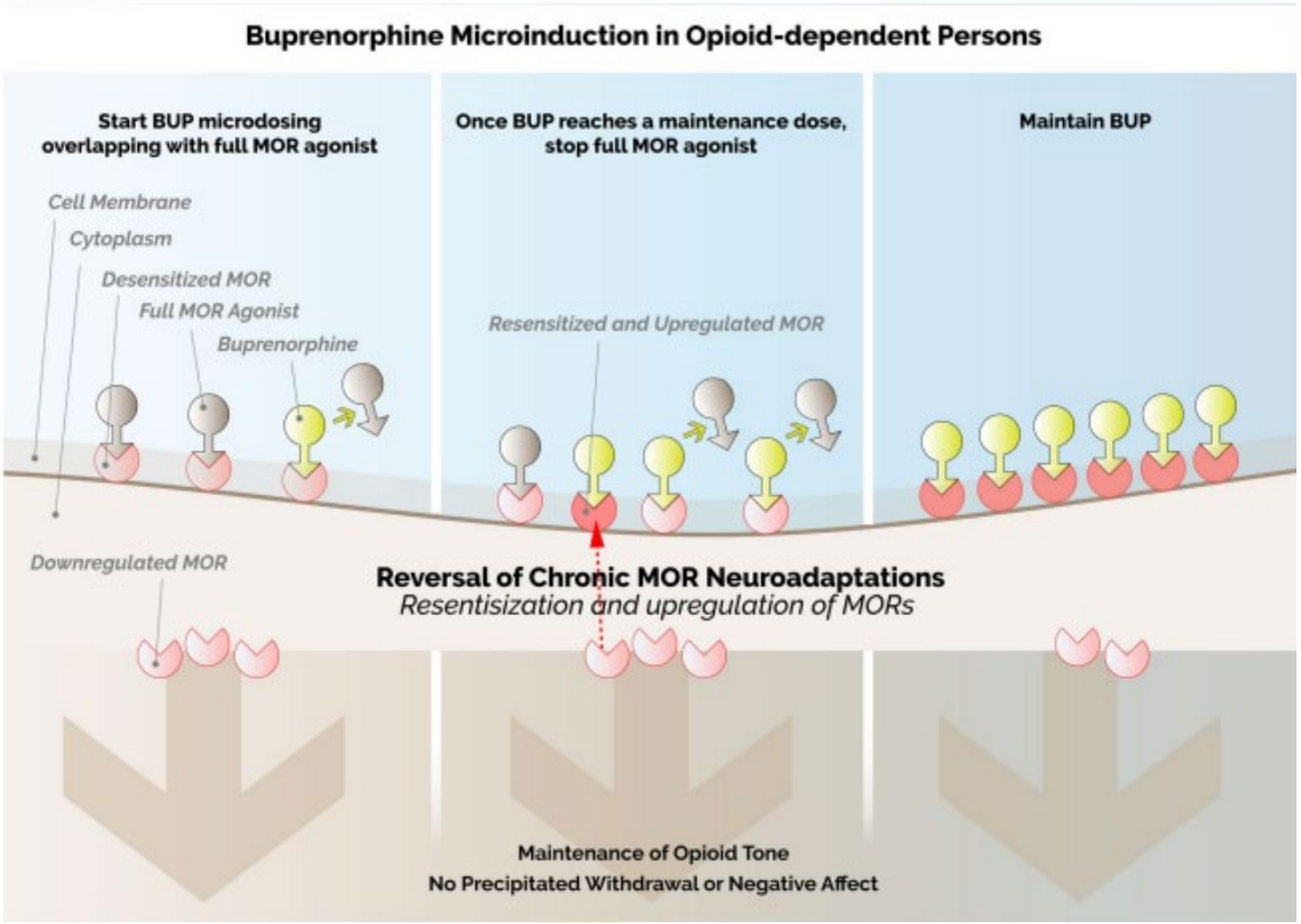
De Aquino JP, et al. Clin Drug Investig. 2021 May;41(5):425-436.

Micro-Induction Effects



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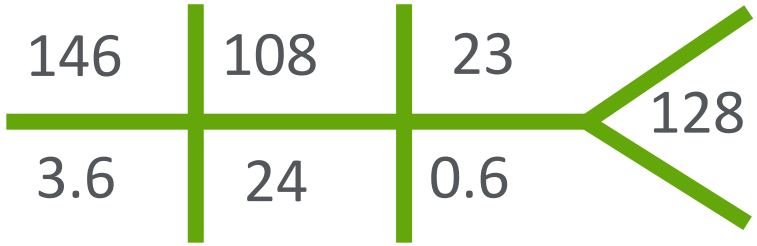
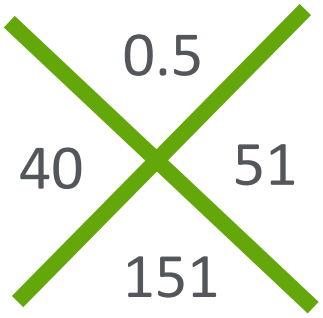
De Aquino JP et al. Clin Drug Investig. 2021 May;41(5):425-436.
Dang, et al. Br J Pharmacol. 2012 Mar;165(6):1704-1716.

SJH Patient Case

- 28 YOM intubated at OSH for AHRF after being diagnosed with tricuspid valve endocarditis and bilateral cavitary lung lesions
- PMH: asthma, HCV, IVDU, and polysubstance use
- Operative Interventions:
  - 9/2: Splenectomy
  - 9/8: Tracheostomy
  - 9/14: Tricuspid and aortic valve AngioVac
- 9/7 Labs:





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SJH Patient Case (Cont'd)

- Pharmacy consulted to start BUP therapy 9/7

	Buprenorphine – Naloxone Dosing	BUP Total Daily Dose	Ketamine Infusion (mg/kg/hr)	Midazolam Infusion (mg/hr)	Fentanyl Patch Strength (mcg/hr)
Day 1 (vent day 15)	0.5 mg SL q6h	2 mg	2.5 mg/kg/hr	20 mg/hr	75 mcg/hr
Day 2 (vent day 16)	1 mg SL q6h	4 mg	1 mg/kg/hr	18 mg/hr	75 mcg/hr
Day 3 (vent day 17)	2 mg q6h	8 mg	1.5 mg/kr/hr	18 mg/hr	75 mcg/hr
Day 4 (vent day 18)	12 mg x1	12 mg	1 mg/kg/hr	10 mg/hr	50 mcg/hr
Day 5 (vent day 19)	16 mg x1	16 mg	1 mg/kg/hr	8 mg/hr	50 mc/hr

- Ketamine and midazolam discontinued 9/13
- Fentanyl patch tapered and discontinued 9/21

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Transmucosal BUP Formulations & Administration

- Suboxone (buprenorphine-naloxone):
  - Sublingual tablets and films
- Zubsolv (buprenorphine-naloxone):
  - Sublingual tablets
- Bunavail (buprenorphine-naloxone):
  - Buccal films
- Subutex (buprenorphine):
  - Sublingual tablets and films

- With the exception of Bunavail, all forms administered by placing directly under patient's tongue
- Safe to cut formulations for precise dosing

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Reindel KL ,er al. *Int J Pharm Compd*. 2019;23(3):258-263.

Kentucky MOUD Regulations

- 201 KAR 9:270
- Physicians or mid-level providers may utilize BUP or methadone products for in-patient detoxification without obtaining a DATA 2000 waiver or “X waiver”
- DATA 2000 waiver or “X-waiver” pertains to BUP prescribing only, as outpatient methadone is exclusively dispensed in outpatient treatment programs
- Without a waiver, may treat up to 30 patients at once with BUP
- Patients with a non-OUD admitting diagnosis + incidental OUD are eligible for MOUD treatment

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Title 201 Chapter 9 Regulation 270 • Kentucky Administrative Regulations • Legislative Research Commission, 2021

Kentucky Regulations: Initiation

- 201 KAR 9:270
- Initiate buprenorphine treatment under an observed induction protocol
- Maximum initial dose: BUP 4 mg
  - May provide subsequent doses if withdrawal persists
- Maximum subsequent doses (cumulative): BUP 24 mg

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Title 201 Chapter 9 Regulation 270 • Kentucky Administrative Regulations • Legislative Research Commission, 2021

Kentucky Regulations: Formulations

- Buprenorphine-mono-products **may** be administered if:
  - Patient is pregnant
  - Demonstrated hypersensitivity to naloxone
  - In a supervised hospital setting

- Only buprenorphine products with an FDA labeled indication for OUD treatment may be used
  - Cannot use Butrans patches, Buprenex injection, or Belbuca buccal formulations (all have chronic pain indications)

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Title 201 Chapter 9 Regulation 270 • Kentucky Administrative Regulations • Legislative Research Commission, 2021

Kentucky Regulations: BUP Split-Dosing

- After initial induction is established, split-dosing is only allowed in specific situations
- Pregnancy: taken no more than BID
- Daily dose < 16 mg: taken no more than BID
- Cancer treatment, hospice or palliative care: taken BID or TID
- Undergoing major surgery or has suffered a significant physical trauma that has a risk of death, physical disability or impairment: taken BID or TID up to 14 days

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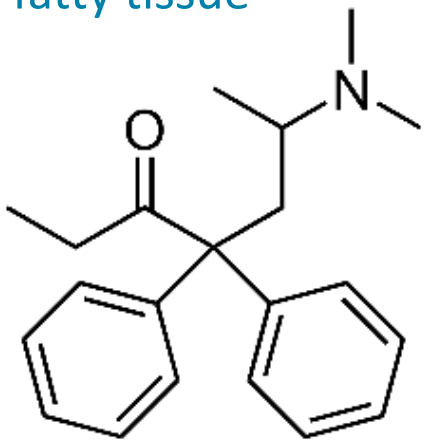
Title 201 Chapter 9 Regulation 270 • Kentucky Administrative Regulations • Legislative Research Commission, 2021

Methadone

- Synthetic opioid & full μ-opioid receptor agonist
- Initial Daily Dose: 10-30 mg/day in divided doses
- Hepatically metabolized via CYP enzymes
  - No active metabolites
- Peak effect within 3-5 days of continuous dosing
- Half-life: 12-59 hours
  - High lipophilicity resulting in redistribution into fatty tissue



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Methadone Therapy

- Does not require a specific level of withdrawal to initiate
- Obtain a baseline QTc prior to starting
  - Do not initiate if > 500 msec
- Watch for serotonergic drug-drug interactions
- Increase dose by 5 mg every 3-5 days based on withdrawal and craving symptoms
- Maintenance Dose: 60-120 mg/day

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Methadone Considerations

- Patient must present to an outpatient federally-approved methadone clinic daily for observed dosing
- Delayed onset and requires a slow titration
- Potentially a better option for chronic pain patients
- Risk of QTc prolongation
    - ICU patients often have electrolyte abnormalities
- Metabolized by numerous CYP enzymes and influences serotonin, must consider DDIs

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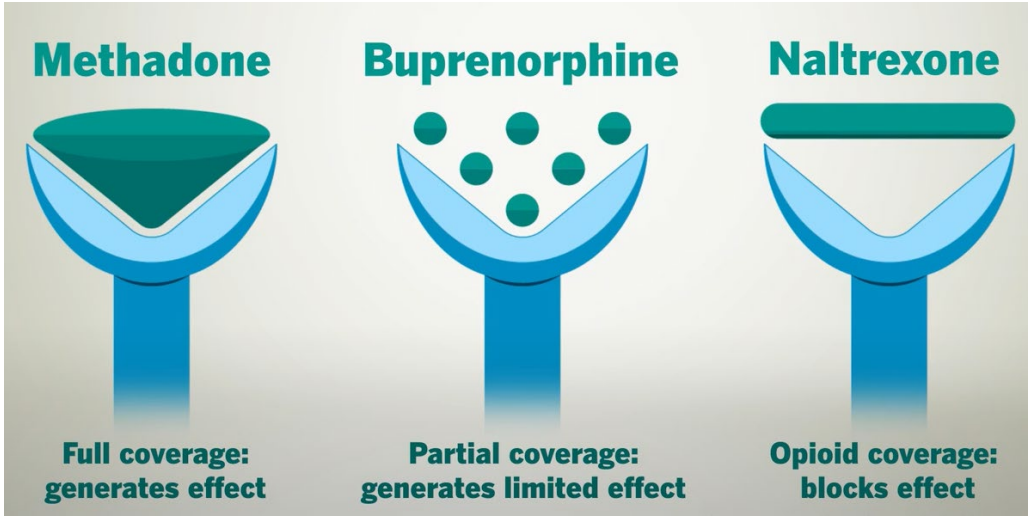
Buprenorphine vs. Methadone

- Appear equally effective in treating OUD
  - Limited data
- Methadone is more difficult for the patient to obtain outpatient
- Buprenorphine maintenance doses are achieved more rapidly
- Neither require active withdrawal
- Fewer ADRs, DDIs, and monitoring with buprenorphine



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Transition of Care at Discharge

- If patient is a new start and does not have an outpatient clinic to follow up with, pharmacy and case management can help facilitate bridge-provider services

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Summary

- As OUD continues to be a leading cause of mortality in the US, the ICU is an appropriate setting to begin MOUD
    - MOUD may also facilitate weaning of IV sedatives/analgesics
- BUP is a partial μ-opioid receptor agonist and κ-opioid receptor antagonist that provides withdrawal and pain relief, with a ceiling effect on respiratory depression
- Rapid micro-inductions are an effective and safe alternative to begin therapy while on full μ-opioid receptor agonists, without fear of precipitating withdrawal

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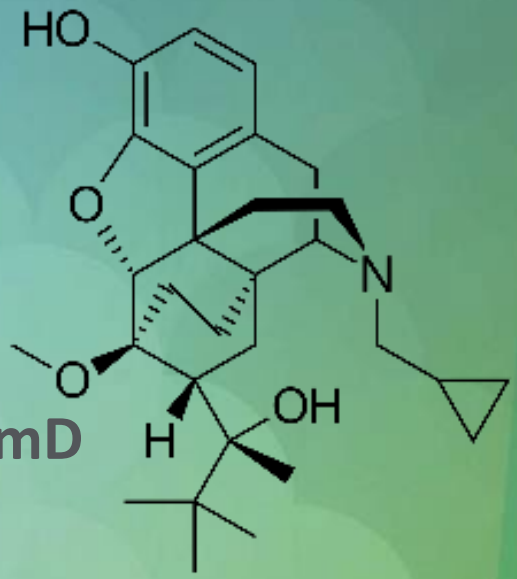
Opioid Stewardship Program Coordinator

Saint Joseph Hospital



Additional Slide Credit: Abbigail Collins, PharmD

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