ACUTE WITHDRAWAL CONSIDERATIONS

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OBJECTIVES: UTILIZE A CASE-BASED APPROACH TO-

- **Review management of common withdrawal syndromes**
  - Alcohol Use
  - Opioid Use
  - Benzodiazepine Use
  - Sympathomimetic Use (Methamphetamine, Cocaine)

- **Consideration of management options for complex withdrawal syndromes**
  - Severe Alcohol Withdrawal Syndrome
  - Precipitated Opioid Withdrawal Syndrome
    - Methadone
    - Buprenorphine
  - Polysubstance Use & Commitment Withdrawal

LIMITATIONS

- Despite common/overlapping institutional practice patterns, evidence is lacking regarding "ideal," management in many clinical situations
- Conscious and unconscious bias/stigma among interactions with patients with substance use
- Developing conversation about the role of the Emergency Department as "missed opportunity" for Opioid, Alcohol and Polysubstance Use

CASE 1:

45 year old male with PMHx HTN, AUD (6 beers each night) presents to the ED seeking assistance with sobriety. 6 months prior attempted to stop "Cold Turkey," however, developed chest pain and anxiety and began consuming alcohol again.

CASE 1 DISCUSSION

How can we assess and classify Alcohol Withdrawal?

Verbal/Responsive: CIWA-Ar for Alcohol Withdrawal (Clinical Institute Withdrawal Assessment for Alcohol)
Pros: Fast beside assessment (< 5 min), Validated (less over sedation in mild withdrawal, shorter hospitalizations, lower incidence of hospitalization)

Absent to Minimal Withdrawal : ≤8
Mild to Moderate Withdrawal: 9-19
Severe Withdrawal: ≥20

Cons: Subjective Scoring, unable to use in non-verbal (intubated, AMS)

Nausea/vomiting

Ask 'Do you feel sick to your stomach? Have you vomited?'

No nausea and no vomiting	0
Mild nausea and no vomiting	+1
(More severe symptoms)	+2
(More severe symptoms)	+3
Intermittent nausea with dry heaves	+4
(More severe symptoms)	+5
(More severe symptoms)	+6
Constant nausea, frequent dry heaves and vomiting	+7

Tremor

Arms extended and fingers spread apart

No tremor	0
Not visible, but can be felt fingertip to fingertip	+1
(More severe symptoms)	+2
(More severe symptoms)	+3
Moderate, with patient's arms extended	+4
(More severe symptoms)	+5
(More severe symptoms)	+6
Severe, even with arms not extended	+7

Paroxysmal sweats

No sweat visible	0
Barely perceptible sweating, palms moist	+1
(More severe symptoms)	+2
(More severe symptoms)	+3
Beads of sweat obvious on forehead	+4
(More severe symptoms)	+5
(More severe symptoms)	+6
Drenching sweats	+7

Anxiety

Ask, 'Do you feel nervous?'

No anxiety, at ease	0
Mildly anxious	+1
(More severe symptoms)	+2
(More severe symptoms)	+3
Moderately anxious, or guarded, so anxiety is inferred	+4
(More severe symptoms)	+5
(More severe symptoms)	+6
Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	+7

Agitation

Normal activity	0
Somewhat more activity than normal activty	+1
(More severe symptoms)	+2
(More severe symptoms)	+3
Moderately fidgety and restless	+4
(More severe symptoms)	+5
(More severe symptoms)	+6
Paces back and forth during most of the interview, or constantly thrashes about	+7

Auditory disturbances

Ask, 'Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?'

Not present	0
Very mild harshness or ability to frighten	+1
Mild harshness or ability to frighten	+2
Moderate harshness or ability to frighten	+3
Moderately severe hallucinations	+4
Severe hallucinations	+5
Extremely severe hallucinations	+6
Continuous hallucinations	+7

Visual disturbances

Ask 'Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?'

Not present	0
Very mild sensitivity	+1
Mild sensitivity	+2
Moderate sensitivity	+3
Moderately severe hallucinations	+4
Severe hallucinations	+5
Extremely severe hallucinations	+6
Continuous hallucinations	+7

Headache/fullness in head

Ask 'Does your head feel different? Does it feel like there is a band around your head?' Do not rate for dizziness or lightheadedness. Otherwise, rate 'severity.'

Not Present	0
Very mild	+1
Mild	+2
Moderate	+3
Moderately severe	+4
Severe	+5
Very severe	+6
Extremely severe	+7

Orientation/clouding of sensorium

Ask 'What day is this? Where are you? Who am I?'

Oriented, can do serial additions	0
Can't do serial additions or is uncertain about date	+1
Disoriented for date by no more than 2 calendar days	+2
Disoriented for date by more than 2 calendar days	+3
Disoriented to place or person	+4

CASE 1 DISCUSSION

How can we assess and classify Alcohol Withdrawal?

Unable to Respond to Questions: Modified Minnesota Detoxification Scale (mMINDS)

Pros: Incorporates physiological variables

Cons: No standardized protocols, RCCTs

Modified Minnesota Detoxification Scale (MINDS)	
PARAMETER (Patient receives score based on real-time assessment)	**SCORE**
Pulse (beats per minute)	
<90	0
90-110	1
>110	2
DIASTOLIC blood pressure (mmHg)	
<90	0
90-110	1
>110	2
***Tremor** – Assess with patient's arms extended and fingers spread.	
Absent	0
Slightly visible or can be felt fingertip to fingertip	2
Moderate – Noticeably visible with arms extended	4
Severe – Noticeable even with arms not extended	6

Sweat	
Absent	0
Barely; Moist palms	2
Beads visible	4
Drenching	6
***Hallucinations** – Feeling crawling sensations over skin (tactile), hearing voices when no one has spoken (auditory), or seeing patterns, lights, beings, or objects that are not there (visual).	
Absent	0
Mild – Mostly lucid, sporadic/rare hallucinations	1
Moderate/Intermittent – Hallucinating at times (when first waking up or in between conversations/patient care) with moments of lucidity but able to be reoriented	2
Severe, continuous while awake	3
***Agitation** – Assess using the Richmond Agitation-Sedation Scale (RASS)	
Normal activity or sedated (RASS of 0 or less)	0
Somewhat > normal (RASS of +1)	3
Moderately fidgety, restless (RASS of +2)	6
Pacing, thrashing (RASS of ≥+3)	9

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Somewhat > normal (RASS of +1)	3
Moderately fidgety, restless (RASS of +2)	6
Pacing, thrashing (RASS of ≥+3)	9
***Orientation**	
Oriented x3 (person/place/time OR at patient's baseline OR too sedated to assess orientation)	0
Oriented x2	2
Oriented x1	4
Disoriented	6
***Delusions** – Unfounded ideas that can be related to suspicions or paranoid thoughts, i.e patient believes their things have been stolen, or they are being persecuted unjustly	
Absent or unable to assess	0
Present	6
Seizures	
Not actively seizing	0
Actively seizing	6
TOTAL	
***If unable to assess a parameter secondary to over sedation or mechanical ventilation, score = 0**	

CASE 1:

45 year old male with PMHx HTN, AUD (6 beers each night) presents to the ED seeking assistance with sobriety. 6 months prior attempted to stop "Cold Turkey," however, developed anxiety and began consuming alcohol again.

CIWA is currently < 8.

Safe for Ambulatory/Discharge Home with Self-Administered Medications?

- No history withdrawal delirium, seizures, ICU admission
- Low CIWA score (< 8-15)
- Low comorbid features/complex PMHx
- Appropriate Return Precautions/Outpatient Follow-Up

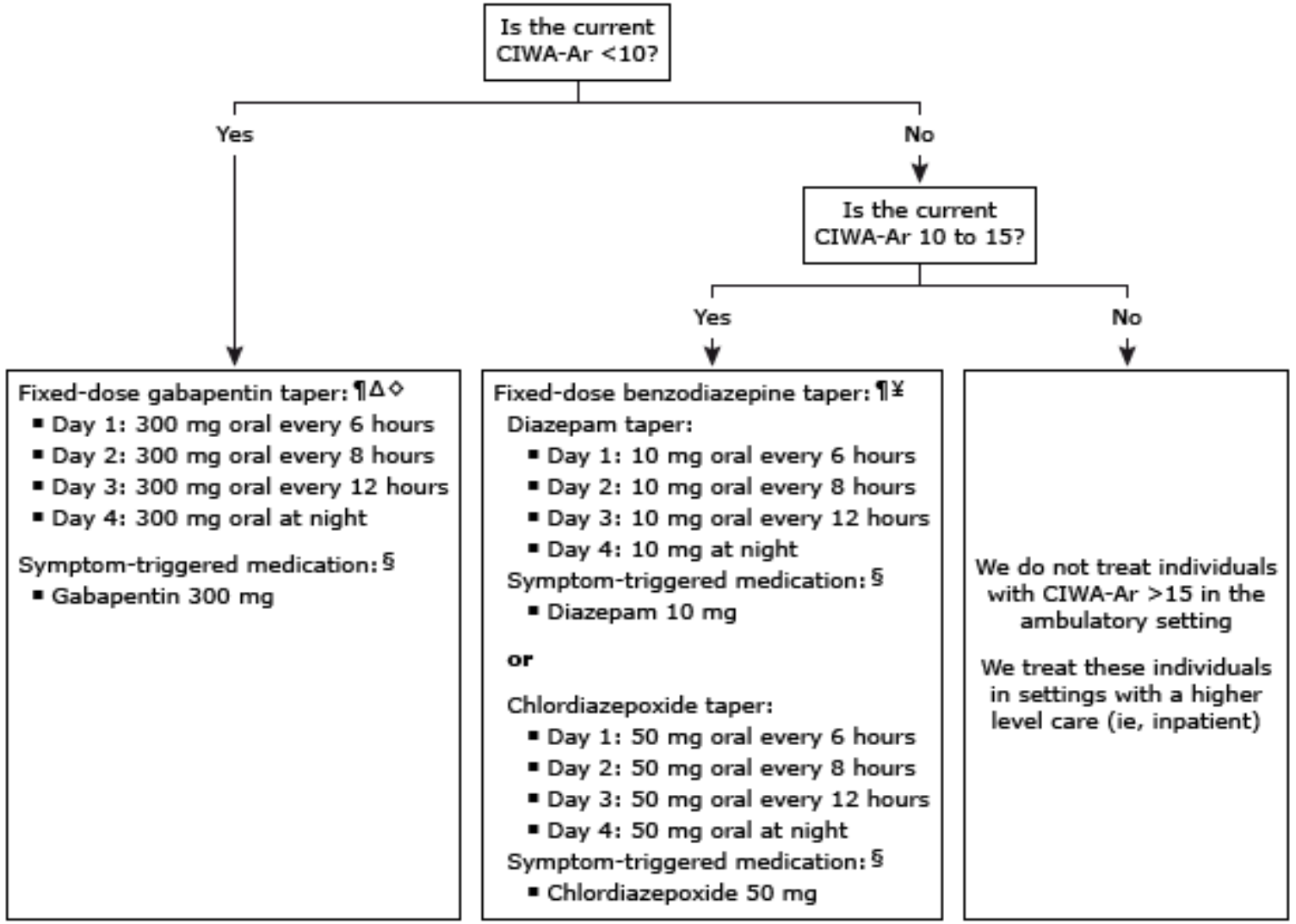
CASE 1:

Ambulatory/Discharge Home with Self-Administered Medications:

<u>Outpatient Withdrawal Treatment Options:</u>

- Gabapentin (proposed MOA increased GABA)
- Benzodiazepine Taper

CASE 1:


Is the current CIWA-Ar <10?
Yes
No
Is the current CIWA-Ar 10 to 15?
Yes
No
Fixed-dose gabapentin taper: ¶Δ◇
Day 1: 300 mg oral every 6 hours
Day 2: 300 mg oral every 8 hours
Day 3: 300 mg oral every 12 hours
Day 4: 300 mg oral at night
Symptom-triggered medication: §
Gabapentin 300 mg
Fixed-dose benzodiazepine taper: ¶¥
Diazepam taper:
Day 1: 10 mg oral every 6 hours
Day 2: 10 mg oral every 8 hours
Day 3: 10 mg oral every 12 hours
Day 4: 10 mg at night
Symptom-triggered medication: §
Diazepam 10 mg
or
Chlordiazepoxide taper:
Day 1: 50 mg oral every 6 hours
Day 2: 50 mg oral every 8 hours
Day 3: 50 mg oral every 12 hours
Day 4: 50 mg oral at night
Symptom-triggered medication: §
Chlordiazepoxide 50 mg
We do not treat individuals with CIWA-Ar >15 in the ambulatory setting
We treat these individuals in settings with a higher level care (ie, inpatient)

CASE 1:

Ambulatory/Discharge Home with Self-Administered Medications:

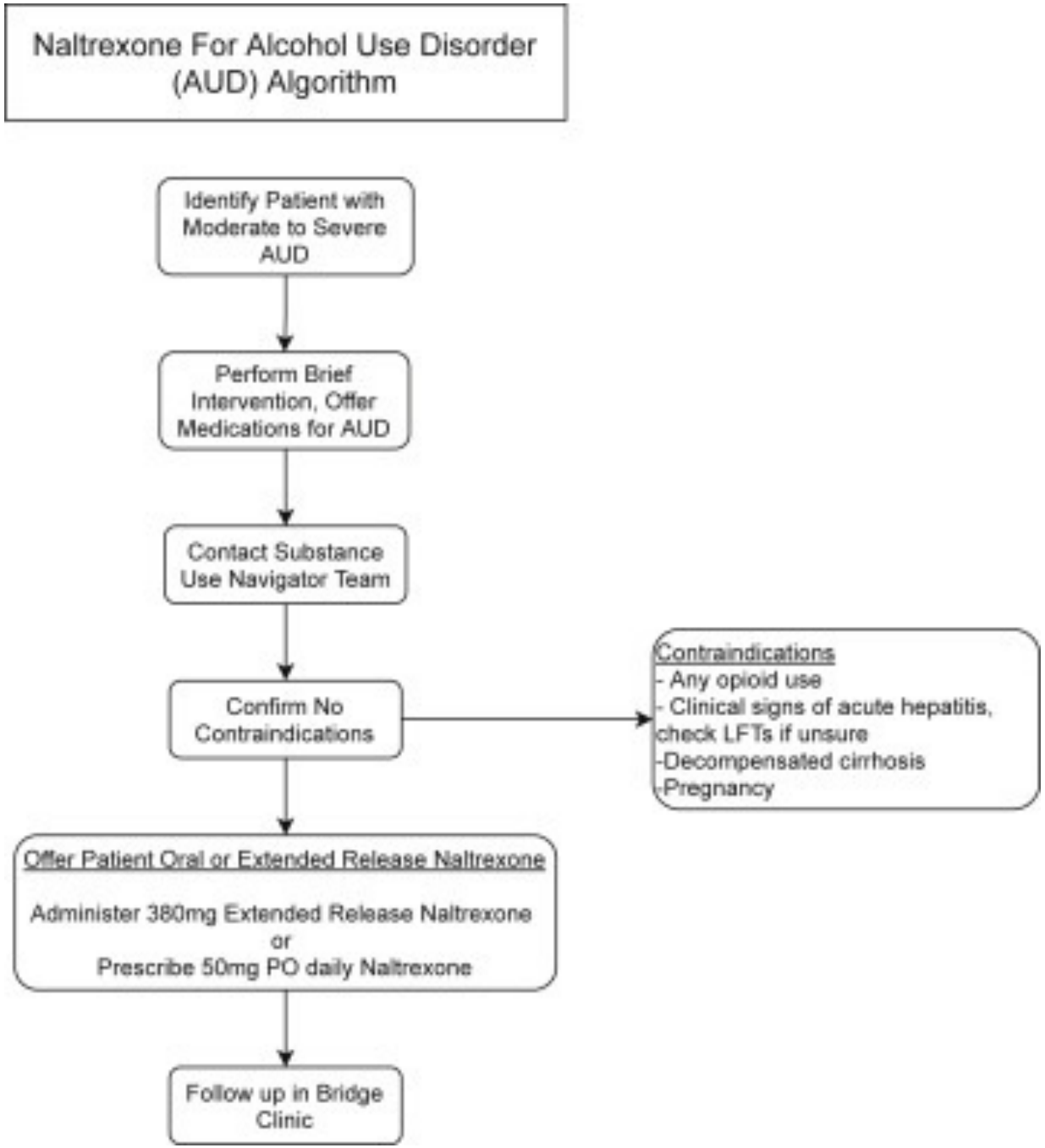
Additional Medications

- Reduces alcohol consumption, return to heavy drinking, total drinking days
- Does **not** prevent withdrawal

- Naltrexone (IM qMonth or PO)
  - Proposed MOA via Mu-Opioid Receptor Blockade
  - May begin treatment while patient still consuming alcohol
- Acamprosate (PO)
  - Proposed MOA via modulation of glutamate neurotransmission
  - Safe for use in those with hepatic disease
  - Appropriate for patients using both alcohol and opioids

"IMPLEMENTATION OF ORAL AND EXTENDED-RELEASE NALTREXONE FOR THE TREATMENT OF EMERGENCY DEPARTMENT PATIENTS WITH MODERATE TO SEVERE ALCOHOL USE DISORDER: FEASIBILITY AND INITIAL OUTCOMES." *ANNALS OF EMERGENCY MEDICINE* (2021)

15% FOLLOW-UP RATE IN FORMAL ADDICTION TREATMENT.



CASE 2:

45 year old male with PMHx HTN, AUD (6 beers each night) presents to the ED seeking ED seeking assistance with sobriety. 6 months prior attempted to stop "Cold Turkey," however, developed severe hallucinations and ultimately had one seizure.

CIWA currently 24

CASE 2 DISCUSSION

Moderate to Severe Withdrawal

- CIWA > 8-15 & mMINDs
  - Benzodiazepines
  - Barbiturates (Phenobarbital, perhaps shorter ICU stay, incidence and duration of MV)?

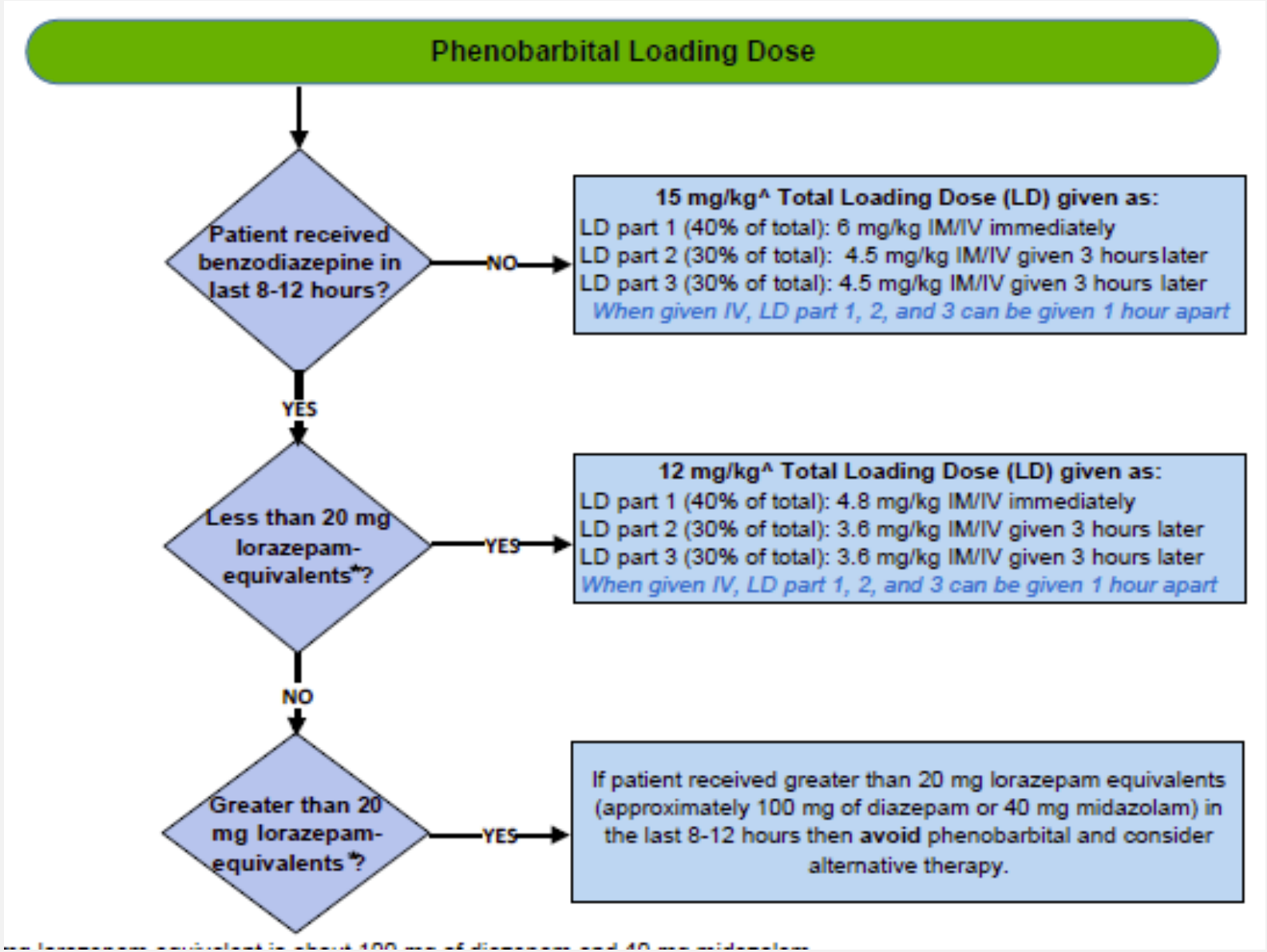
Is "Monotherapy," needed? vs multi-modal?

- Benzodiazepines + Gabapentin (reduces total benzodiazepines, LOS)?
- Gabapentin + Baclofen (GABA-agonist, perhaps shorter LOS) ?
- +/- Dexmedetomidine (Precedex, improved CIWA)

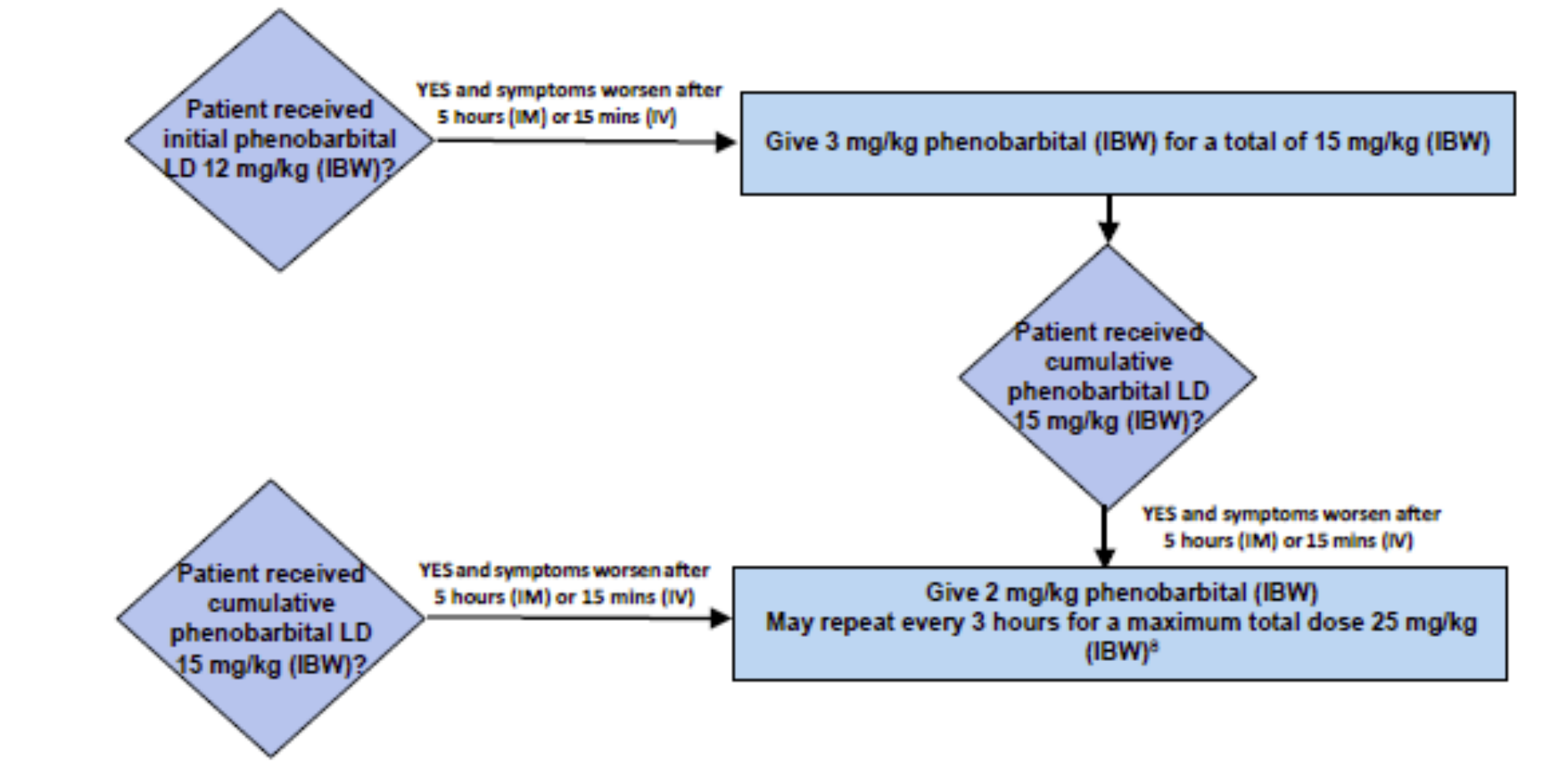
CASE 2: PERSONAL BIAS/PRACTICE

Moderate to Severe Alcohol Withdrawal

- I personally use IM or IV Phenobarbital



CASE 2: PERSONAL BIAS/PRACTICE



CASE 4:

52 year old female with PMHx generalized anxiety disorder, depression, PTSD presents with tachycardia, concern for "severe anxiety." She has been traveling and ran out of her prescription lorazepam (1 mg TID) 3 days previously.

CASE 4 DISCUSSION

Benzodiazepine Withdrawal

- Withdrawal symptoms can over develop over a period of 1 day – 3 weeks

- Consider giving prescription *or usual used dose* to treat withdrawal
- For severe symptoms IV Benzodiazepines
- Plan on initiating prescription benzodiazepine taper
  - 4 -16 weeks taper

  No great evidence for adjuvant therapy

CASE 5:

42 year-old-male with PMHx substance use (cocaine, methamphetamine) presents with suicidal ideation, abdominal discomfort and inability to sleep for 4 days. He has stopped using cocaine in the setting of significant behavioral concerns from coworkers and family members.

CASE 5 DISCUSSION

Sympathomimetic/Stimulant Withdrawal & Cessation

- Monitor for increased risk of depression, anxiety
- ”Serious,” symptoms rare, however, include seizure

- Cocaine Use Disorder:
  - “Supportive,” care and close psychosocial treatment
    - Propranolol (proposed to reduce anxiety due to decreasing activity of noradrenergic receptors)
    - Topiramate (GABA agonism, inhibits glutamate)
    - Developing evidence regarding long-acting stimulants and amphetamines (modafinil)

CASE 5 DISCUSSION

Sympathomimetic/Stimulant Withdrawal & Cessation

- Methamphetamine Use Disorder:
  - "Supportive," care and close psychosocial treatment
    - Bupropion with naltrexone?
    - Mirtazapine?
  - *"What is our (ED) role in treating…?"*

CASE 6:

68 year-old-male with PMHx AUD (hx of withdrawal seizures requiring intubation) , HTN, AFib, DM, COPD with AFib w/RVR, acute agitation. HR irregularly irregular 120-150, BP 110/50.

CIWA is initiated and after multiple doses of IV benzodiazepines..

Telemetry shows AFIB w/rates 150-180.

Patient is dangerously striking out with inability to follow redirection..

CASE 6 DISCUSSION-WHERE WE LOSE OUR MINDS

Patient is intubated without event, however, is hypertensive w/persistent AFIB w/RVR.

mMINDS is > 40

"Refractory Delirium Tremens"

Options:

- +/- Benzodiazepine infusion
- +/- Propofol
- +/- Phenobarbital (130 mg-260 mg IV q 15 minutes) or perhaps load w/15 mg/kg?
- +/- Dexmedetomidine

CASE 7:

32 year old female presents with abdominal pain, nausea, vomiting, diarrhea. She actively uses heroin and desires to stop use. Her last use was 2 days previously.

- ED-Based Initiation of Buprenorphine (partial mu opioid agonist)
  - COWS Score is 10

GI Upset
Over last 0.5 hours

No GI symptoms	0
Stomach Cramps	+1
Nausea or loose stool	+2
Vomiting or diarrhea	+3
Multiple episodes of vomiting or diarrhea	+5

Tremor observation of outstretched hands

No tremor	0
Tremor can be felt, but not observed	+1
Slight tremor observable	+2
Gross tremor or muscle twitching	+4

Yawning observation during assessment

No yawning	0
Yawning once or twice during assessment	+1
Yawning three or more times during assessment	+2
Yawning several times/minute	+4

Resting Pulse Rate (BPM)
Measure pulse rate after patient is sitting or lying down for 1 minute

≤80	0
81-100	+1
101-120	+2
>120	+4

Sweating
Sweating not accounted for by room temperature or patient activity over the last 0.5 hours

No report of chills or flushing	0
Subjective report of chills or flushing	+1
Flushed or observable moistness on face	+2
Beads of sweat on brow or face	+3
Sweat streaming off face	+4

Restlessness observation during assessment

Able to sit still	0
Reports difficulty sitting still, but is able to do so	+1
Frequent shifting or extraneous movements of legs/arms	+3
Unable to sit still for more than a few seconds	+5

Anxiety or irritability

None	0
Patient reports increasing irritability or anxiousness	+1
Patient obviously irritable/anxious	+2
Patient so irritable or anxious that participation in the assessment is difficult	+4

Gooseflesh skin

Skin is smooth	0
Piloerection of skin can be felt or hairs standing up on arms	+3
Prominent piloerection	+5

Pupil size

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

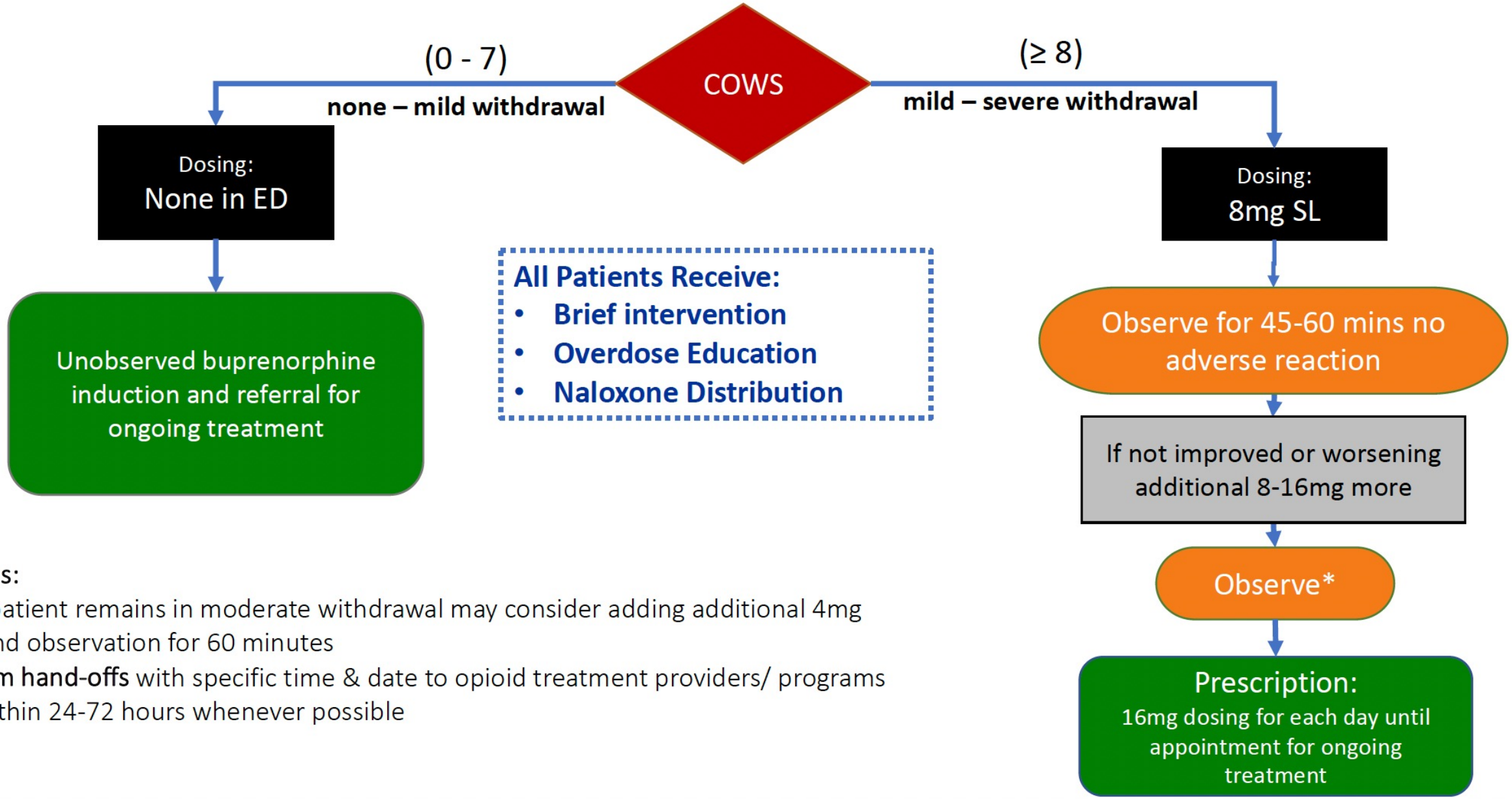
Bone or joint aches
If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored

Not present	0
Mild diffuse discomfort	+1
Patient reports severe diffuse aching of joints/ muscles	+2
Patient is rubbing joints or muscles and is unable to sit still because of discomfort	+4

Runny nose or tearing
Not accounted for by cold symptoms or allergies

Not present	0
Nasal stuffiness or unusually moist eyes	+1
Nose running or tearing	+2
Nose constantly running or tears streaming down cheeks	+4

ED-Initiated Buprenorphine



Notes:

* If patient remains in moderate withdrawal may consider adding additional 4mg and observation for 60 minutes

Warm hand-offs with specific time & date to opioid treatment providers/ programs within 24-72 hours whenever possible

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

8 mg

Wait 45 minutes

- 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

4 mg

Wait 6 hours

Most people feel better after 8-16 mg

Step 3.

Still uncomfortable? Take last dose

4mg

Stop

- Stop after this dose

DAY 2:

16-24 mg of buprenorphine

Take one 16mg dose

Most people feel better with 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

Strategies for ED Buprenorphine Initiation

- Standard ED Dosing
- High Dose
- Low Dose
- Injectable Formulations

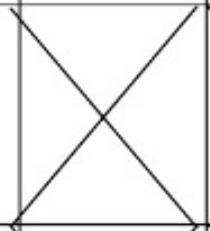
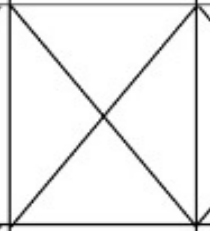
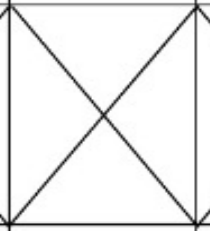
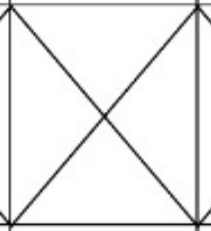
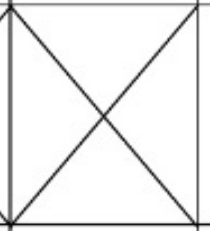
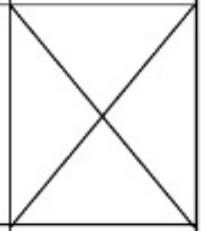
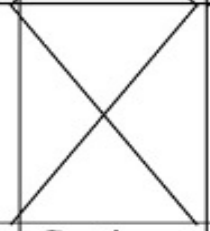
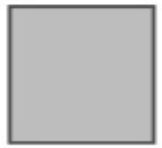
RATIONALE FOR LOW DOSE

- Current opioid agonist treatment for pain
- Current treatment with methadone
- Intolerance to opioid withdrawal
- Concern about precipitated withdrawal

BERNESE METHOD

A

Dosing Guide for an example low dose initiation regimen

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID	2mg BID	4mg BID	4mg TID	8mg BID
Film size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

BID=twice per day
TID=Three times per day

Cohen, etal JAM 2022

LOW DOSE CONSIDERATIONS

- Good success reported in hospitalized patients
- ED specific challenges:
  - Complicated dosing regimen
  - Up to a week before therapeutic BUP dosing
  - The absence of withdrawal relies on ONGOING full agonist exposure (=fentanyl for many ED patients)

Rationale for High Dose

Rapid titration to therapeutic buprenorphine levels

- Minimizing craving and incompletely treated withdrawal

Lasts up to 72 hours

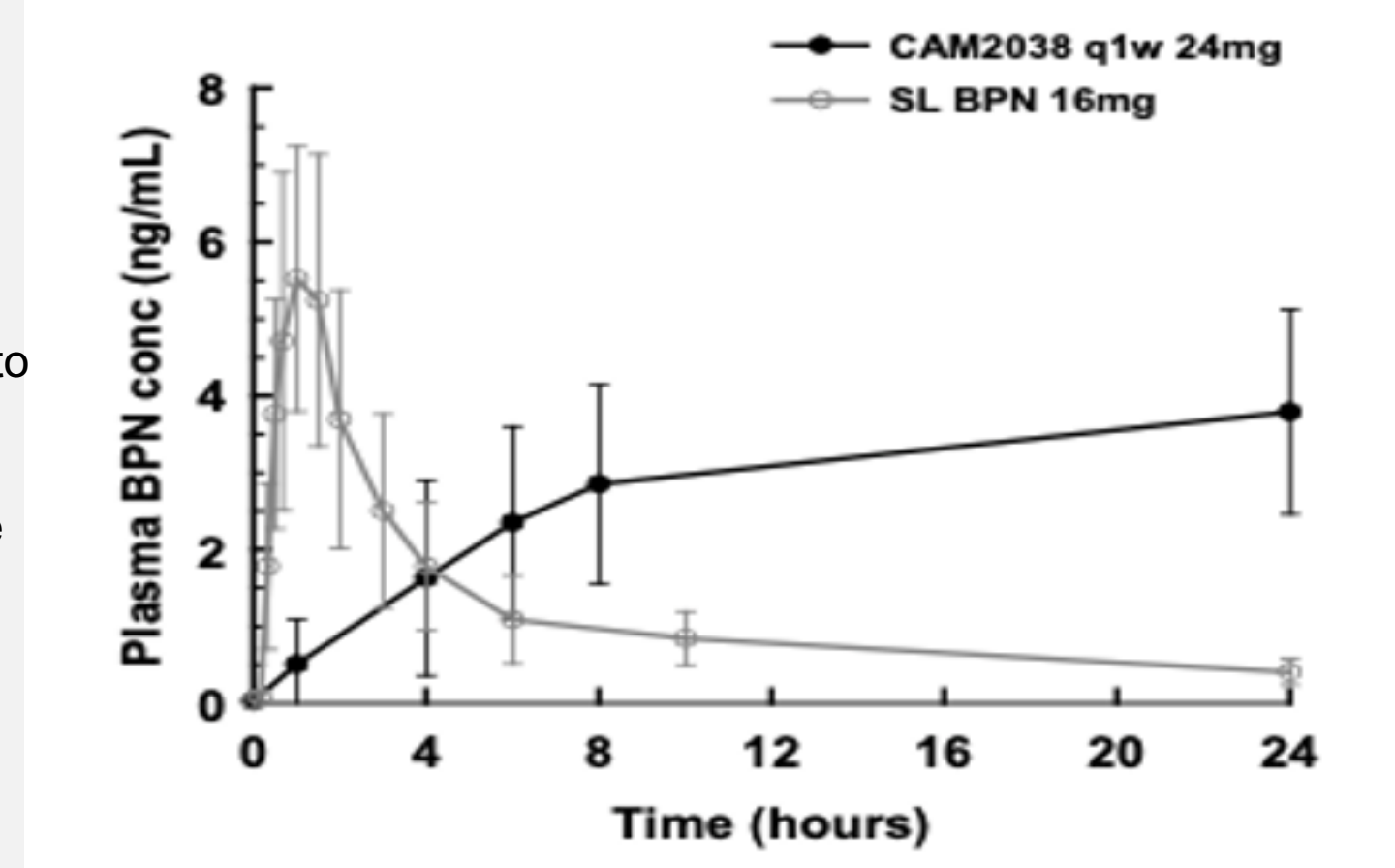
- Providing a safety net if unable to access Rx next day
- May be less true in context of high dose fentanyl use

ED INNOVATION

24mg XR-BUP 7-day injectable vs 16mg SL-BUP per day

Pharmacokinetics of XR- & SL- Buprenorphine

Upon injection **CAM2038** forms into a viscous liquid crystalline gel, producing a sustained, non-fluctuating levels of buprenorphine in the blood **avoiding the peaks and troughs of daily dosing**



3UG1DA015831

ED-INitiated BupreNOrphine VAlidaTION Network Trial

To compare the effectiveness of XR-BUP and SL-BUP induction (8-12mg) in approximately 2000 patients with untreated OUD in the ED on the primary outcome of engagement in formal addiction treatment at 7 days

RCT
1945
enrolled

Lead Investigators

D'Onofrio, Contemporary Clinical Trials, 2021

CASE 8:

32-year-old female presents with abdominal pain, nausea, vomiting, diarrhea. She uses prescription methadone daily and intermittently uses heroin. She was found to be apneic and unresponsive today. She received "multiple doses," naloxone from a bystander and subsequently became alert and agitated.

Her COWS score is 30.

CASE 8 DISCUSSION

- Consider giving portion of home dose Methadone
  - Alternatively, 20–30 mg while monitoring for signs of over sedation, an additional10 mg every 4 hours

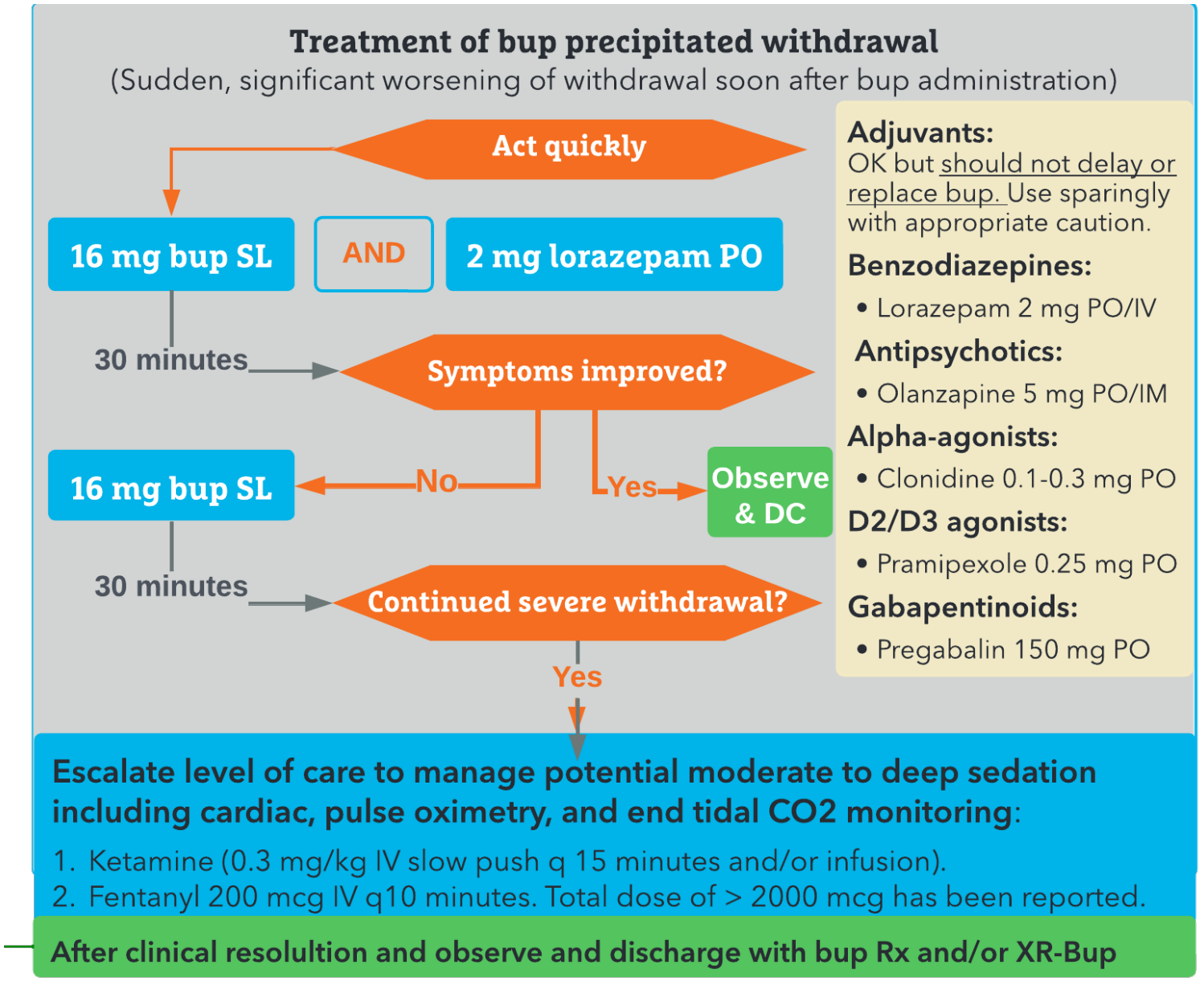
CASE 9:

34 year-old-female with PMHx opioid use disorder presenting to ED requesting assistance with cessation. Initiated on buprenorphine and subsequently develops abdominal pain, nausea and vomiting, diarrhea and anxiety.

CASE 9 DISCUSSION

- Prevention is the BEST treatment.
- Once in PW, the best treatment is buprenorphine
  - 16 mg BUP +/- 1-2 mg lorazepam
  - Repeat 16 mg BUP and/or 0.3 mg/kg ketamine

CASE 8 DISCUSSION



Credit: Andrew Herring

JAMA Network | Open

Research Letter | Substance Use and Addiction

Incidence of Precipitated Withdrawal During a Multisite Emergency Department–Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

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Introduction

Buprenorphine treatment is associated with decreased mortality and morbidity,[1] yet the treatment gap remains wide. Emergency departments (EDs) offer an effective, low-barrier setting in which to initiate buprenorphine.[2] Retrospective case series[3] have raised concerns about increased incidence of precipitated withdrawal (PW) when buprenorphine is initiated in persons using fentanyl, a high-potency μ-opioid agonist with high affinity and slow dissociation from the μ receptor. With long-term use, its high lipophilicity leads to bioaccumulation and prolonged metabolite excretion. As confidence in standard buprenorphine inductions has eroded, alternative strategies, such as low-dose buprenorphine, have emerged, often prompting continued use of illicit opioids. Thus, there is a need for high-quality evidence from prospective studies using uniform surveillance and operational definitions of PW. We report the incidence of PW as part of an ongoing randomized clinical trial[4] comparing traditional sublingual buprenorphine with CAM2038, a 7-day extended-release injectable form of buprenorphine, conducted in sites with high prevalence of fentanyl.

+ Supplemental content

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Buprenorphine induction in the ED remains safe and effective, even with fentanyl present

CASE 10

56 year-old-male with a PMHx AUD (10 shots vodka/day), Polysubstance use (cocaine, benzodiazepines, heroin), Tobacco use disorder (1 PPD), Bipolar Disorder, Major Depressive Disorder presents after being found on the ground outside of a bar. Staff report he had to be forcefully removed from premises after demanding alcohol and not having money to pay for it. Received 4 mg naloxone with resulting agitation, then received IM ketamine from EMS with resulting improved agitation. Noted to have continued altered mental status, sinus tachycardia 130, nausea and vomiting.

CASE 10 DISCUSSION

Polysubstance use with concurrent intoxication and withdrawal

- Benzodiazepine Infusion?
- Opioid Infusion?
- Propofol Infusion?
- Phenobarbital?
- Methadone Initiation with taper?

ADDITIONAL CONSIDERATIONS

- Critical need for stakeholder & champion engagement across the spectrum of care to develop, study and implement new SUD care protocols
- As healthcare continues to face worsening access to timely healthcare, the ED may be the "only," option for increasingly complex substance use intervention
- Anticipate the rise of increasingly complex polysubstance use disorders with psychiatric comorbidities
- Evidence is severely lacking.

Wado!

Thank you.

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