

Precipitated Withdrawal

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Disclosures

- No relevant financial disclosures
- Will discuss off-label use of clonidine for opioid withdrawal

Objectives

At the end of this lecture participants will be able to:

- Name common signs and symptoms opioid withdrawal
- Understand the mechanism of precipitated withdrawal
- Discuss risk factors of precipitated withdrawal when starting patients on buprenorphine or naltrexone
- Discuss treatment of precipitated withdrawal and some advantages and disadvantages of each approach

Treatment of OUD

- Due to high risk of accidental overdose and death after withdrawal from opioids or from continued opioid use, pharmacotherapy is the standard of care for OUD
 - Buprenorphine
 - Methadone
 - Naltrexone-XR

Treatment of OUD

- To start buprenorphine one needs to be in mild-moderate withdrawal to avoid precipitated withdrawal
- To start naltrexone, one needs to go through withdrawal and start typically 7-10 days after last opioid to avoid precipitated withdrawal
- No withdrawal needed to start methadone, however, caution should be used in starting methadone if patient shows evidence of intoxication

Opioid Withdrawal

- Increased CNS noradrenergic hyperactivity occurs during opioid withdrawal
- This may be responsible for some of the opioid withdrawal symptoms
- Systematic administration of morphine produces inhibition of locus coeruleus cell firing, this can be reversed with naloxone
- Studies in rats and nonhuman primates found noradrenergic activity is markedly increased in opioid withdrawal
- Naloxone and naltrexone precipitated opioid withdrawal results in firing of locus coeruleus
 - Administration of clonidine reduces or prevents increase in firing
 - Clonidine can ameliorate some opioid withdrawal symptoms

Opioid Withdrawal S/S

- Tachycardia
- Dilated pupils, rhinorrhea, tearing, yawning
- Piloerection, tremor
- GI upset (nausea, vomiting, diarrhea)
- Insomnia
- Muscle and joint pain
- Anxiety, irritability, restlessness
- Chills

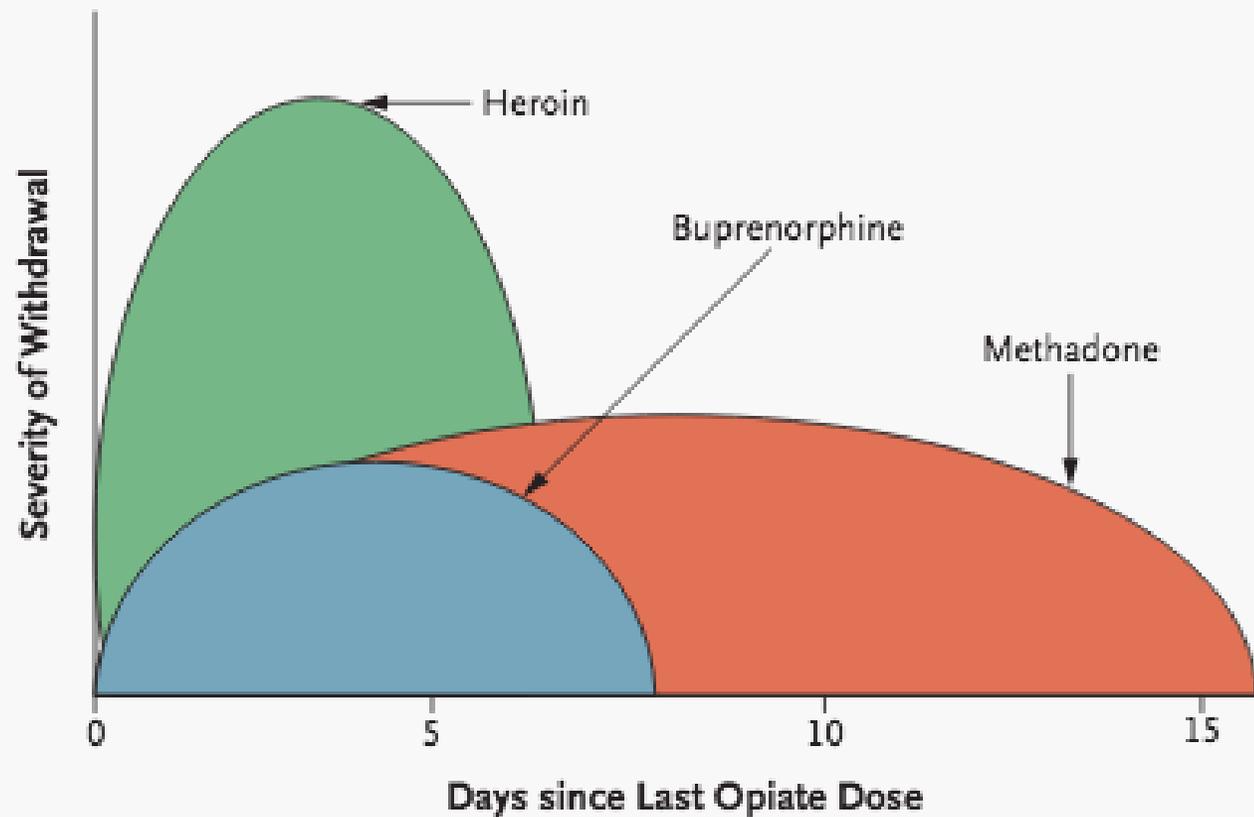


Figure 1. Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone.

Peak withdrawal symptoms are most severe after discontinuation of heroin. Such symptoms last longest with methadone, which has a somewhat later peak of severity. Buprenorphine has milder peak withdrawal symptoms than does methadone; the duration of symptoms is intermediate between those for methadone and those for heroin.

Usual Opioid Withdrawal Timeline

	Grade	S/S	Onset
Early	1	Lacrimation, Rhinorrhea, Diaphoresis, Yawning, Restlessness, Insomnia	4-24 hours after short-acting; up to 36 hours after long-acting opioid
	2	Dilated pupils, Piloerection, Muscle twitching, Myalgia, Arthralgia, Abdominal pain	
Full	3	Tachycardia, Hypertension, Tachypnea, Fever, Anorexia, Nausea, Extreme restlessness	1–3 days after short-acting; 72–96 hours after long-acting
	4	Diarrhea, Vomiting, Dehydration, Hyperglycemia, Hypotension, Curled-up position	

Duration of withdrawal:
 Short-acting 7-10 days
 Long-acting 14+ days

COWS

Patient's Name: _____		Date and Time ____/____/____:_____	
Reason for this assessment: _____			
Resting Pulse Rate: _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120		GI Upset: <i>over last 1/2 hour</i> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting	
Sweating: <i>over past 1/2 hour not accounted for by room temperature or patient activity.</i> 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: <i>observation of outstretched hands</i> 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Restlessness: <i>Observation during assessment</i> 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: <i>Observation during assessment</i> 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 or anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Bone or Joint aches: <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 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 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Runny nose or tearing: <i>Not accounted for by cold symptoms or allergies</i> 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

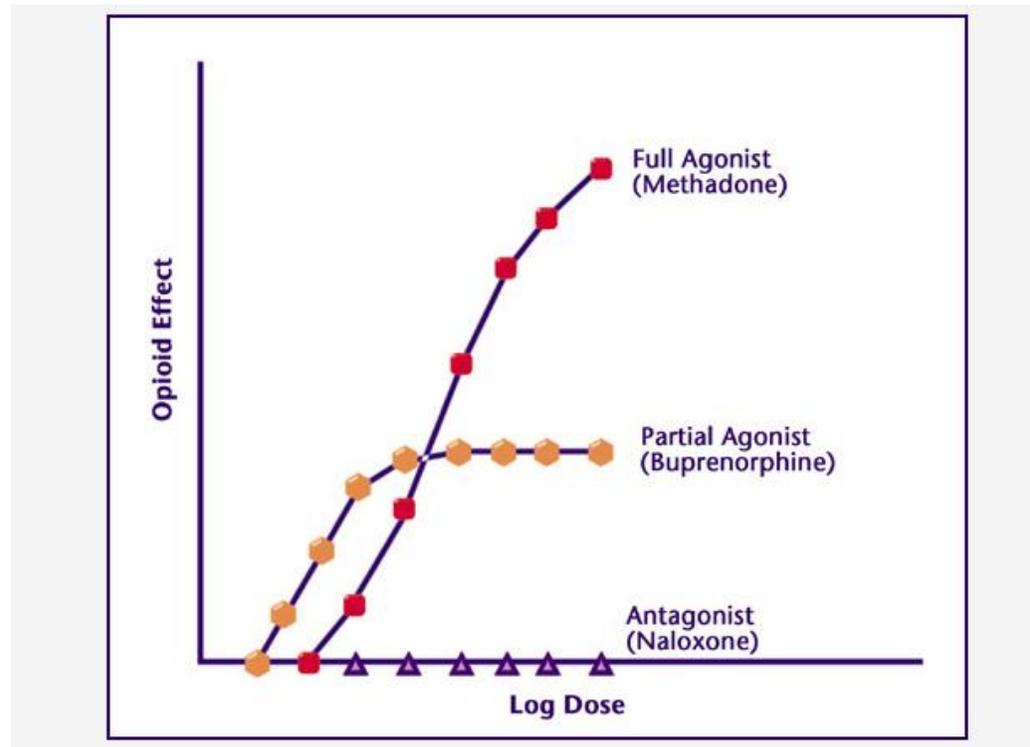
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Precipitated Withdrawal

- Acute worsening of opioid withdrawal symptoms after taking dose of buprenorphine
- Occurs when someone who is physically dependent on opioids, has opioids occupying mu-opioid receptors, and buprenorphine or naltrexone displace opioid agonist
- May occur 30 mins to 3 hours after taking dose
- Concern about precipitated withdrawal is reason for office-based inductions
- Precipitated withdrawal may result in loss to follow-up

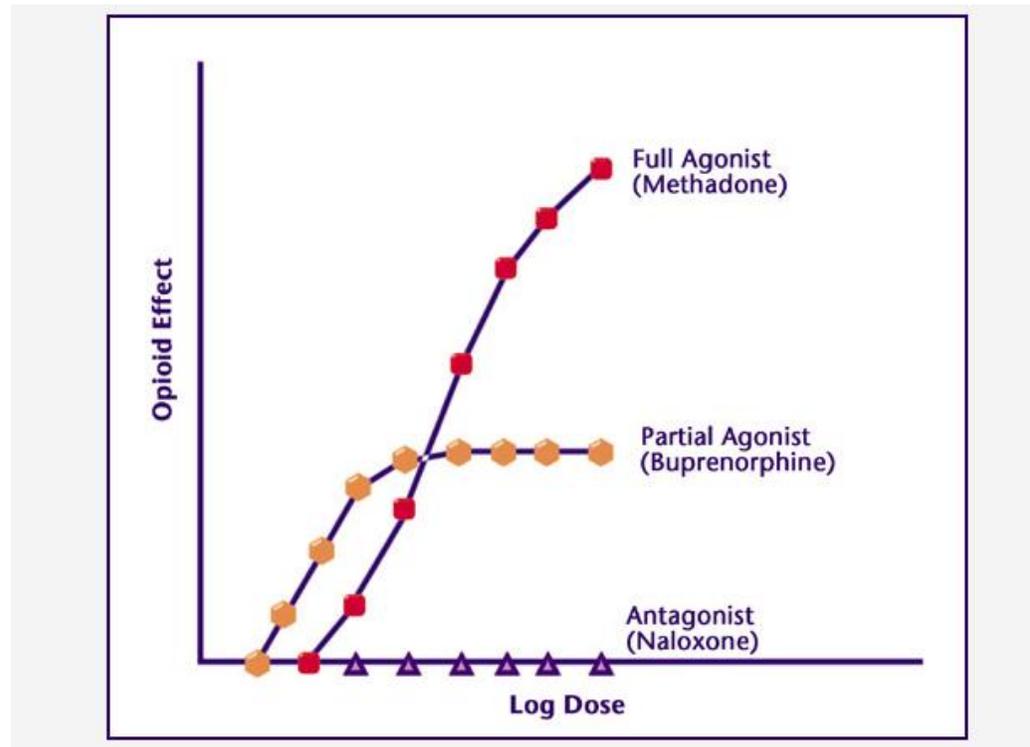
Buprenorphine precipitated withdrawal

- High affinity for mu-opioid receptor
- Low intrinsic agonist activity
- Buprenorphine displaces bound agonist, resulting in net decrease in agonist activity and precipitated withdrawal



Naltrexone precipitated withdrawal

- High affinity for mu-opioid receptor
- No agonist activity
- Naltrexone displaces bound agonist, resulting in net decrease in agonist activity and precipitated withdrawal



Opioid Binding Affinity

Table 5. Mu Receptor Affinities of Various Opioids¹⁹

Opioids	Range of Ki Value
Levorphanol	0.19 to .23 ³²
Buprenorphine	0.21 to 1.5
Naltrexone	0.4 to 0.6 (antagonist effects) ²⁰
Fentanyl	0.7 to 1.9
Methadone	0.72 to 5.6
Naloxone	1 to 3 (antagonist effects) ²⁰
Morphine	1.02 to 4
Pentazocine	3.9 to 6.9
Codeine	65 to 135

Review of Buprenorphine Inductions

- Retrospective review study, buprenorphine inductions from 2005-2008 at a community health center
- 107 initiated buprenorphine (60 office-based, 47 home-based)
- Most commonly used opioid was heroin (68.2%), followed by nonprescribed methadone (30.8%), prescribed methadone (29.9%), prescribed opioid analgesics (16.8%), and nonprescribed opioid analgesics (11.2%)
- 27.1% had prior experience with buprenorphine
- Most started with buprenorphine 2 mg

Review of Buprenorphine Inductions

- 10 people had precipitated withdrawal
 - 9 were taking methadone
 - 2 patients misrepresented their substance use
 - Most common symptom complained of was increased anxiety
 - 6 of the 10 discontinued treatment shortly after induction
- Precipitated withdrawal treated by increasing buprenorphine more rapidly in first 24-28 hours and providing ancillary meds
- Precipitated withdrawal was associated with lower 30-day retention
- Those with precipitated withdrawal were less likely to have had experience with buprenorphine
- Fewer complicated inductions as providers became more experienced

Rates of Precipitated withdrawal

- Study of converting from methadone to buprenorphine in 33 individuals, 3 (9%) experienced precipitated withdrawal (all were on >50 mg methadone) and 7 (21%) returned to methadone within 1 week of transfer (Lintzeris et al., 2018)
- Low threshold program in Norway found 85.2% of patients successfully completed induction and there were no cases of precipitated withdrawal (Henriksen et al., 2018)
- Low threshold office-based treatment in NY performed home-inductions, there were no cases of precipitated withdrawal in the 306 patients who started buprenorphine (Bhatraju et al., 2017)

Case Study #1

- 34 year old woman with OUD, physically dependent on opioids
- In a clinical trial studying withdrawal
- She continued to use opioids throughout the trial
- Urine specimens collected 3 times per week and were positive for opioids
- Received buprenorphine 8 mg daily x3d, then 16 mg on day 4
 - Returned to clinic 90 mins later with opioid withdrawal (CINA = 25)
- Determined to be precipitated withdrawal
- Treated with clonidine and acetaminophen
- Concluded the 8 mg doses of buprenorphine did not result in as much displacement of heroin as did the 16 mg
 - Unsure of the timing of heroin use prior to dosing

Case Study #2

- 34 year old woman with OUD, injecting 2-3 bags of heroin daily x1 year
- No past medical history
- Inconsistent as to last use of heroin
- Initial COWS = 6; administered buprenorphine 4 mg SL x1
- Within 1 hour after buprenorphine 4 mg, she became tachycardic, tachypneic, and diaphoretic
 - Administered buprenorphine 2 mg q2 hrs x2

Case Study #2

- 1 hour after last dose was found to be diaphoretic and dyspneic (BP 124/86, HR 140, RR 25, O2 sat 80%)
- CXR diffuse pulm edema
- EKG showed sinus tachy with anterolateral ST depressions
- Needed intubation, vasopressors
- Had echo, showed global hypokinesis of left ventricle, EF of 10%
- Left and right heart cath was normal; no CAD
- Tnl peaked at 8.7 ng/mL
- Repeat Echo on day 7 showed EF = 65%
- Discharged on day 10 with no sequelae

Case Study #2

- Diagnosis – Takotsubo cardiomyopathy
 - Acute LV systolic dysfunction in response to stress
 - New EKG changes
 - Absence of CAD
 - Relatively small Tn elevation compared to degree of myocardial injury
 - Complete cardiac function recovery
 - No other identifiable cause
- Suspected to be due to surge in plasma catecholamines, often precipitated by stress inducing event, including opioid withdrawal
- Precipitated opioid withdrawal is more severe and rapid than spontaneous opioid withdrawal, which may increase risk

Case Study #3

- 17 year old female
- 2 year history of OUD (pill opioids IN, heroin IN and IV)
- Buprenorphine taper, then 7 days of abstinence from all opioids, started oral naltrexone, received IM naltrexone 5 weeks after starting oral med due to adherence issues
- Tolerated medication
- Reduced use of opioids
- Started testing blockade within a week of first injection using oxycodone IN
 - First week no effect, third week after injection started having mild intox
- Received second injection, tolerated well
- Continued to use oxycodone weekly after injection
- Third injection 2 days after last use of oxycodone

Case Study #3

- The next morning woke with opioid withdrawal symptoms, worsened through the day
 - Vomiting, cramping, sweating
 - Mom took to ED, received IVF and antiemetic
 - Improved over the next two days
 - Five days after naltrexone injection seen in clinic and symptoms completely resolved
- Pt and mom felt the naltrexone was beneficial and elected to continue
- Increased dosing to every 3 weeks to keep higher serum level
- Pt stopped using opioids

Case Study #3

- Studies have shown precipitated withdrawal after a single dose of morphine in rats and humans (typically milder than with chronic dosing)
- Discussed that experiencing opioid effects while receiving injection may indicate need to wait 5-10 days after last use prior to giving injection

Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. *Addiction*. 2008 Aug;103(8):1399-401. doi: 10.1111/j.1360-0443.2008.02252.x. PubMed PMID: 18855831.

Easterling K. W., Holtzman S. G. Discriminative stimulus effects of naltrexone after a single dose of morphine in the rat. *Pharmacol Exp Ther* 1999; **288**: 1269– 77.

Heishman S. J., Stitzer M. L., Bigelow G. E., Liebson I. A. Acute opioid physical dependence in postaddict humans: naloxone dose effects after brief morphine exposure. *J Pharmacol Exp Ther* 1989; **248**: 127– 34.

Schulteis G., Heyser C. J., Koob G. F. Opiate withdrawal signs precipitated by naloxone following a single exposure to morphine: potentiation with a second morphine exposure. *Psychopharmacology* 1997; **129**: 56– 65.



Case Study #4

- 35 year old with 10 year history of heroin use
- Started buprenorphine 8 mg daily, over 3 weeks dose increased to 24 mg daily
- Dosed at pharmacy daily (Australia)
- Weekly urine tox for 6 months indicated no heroin use
- After 12 months of continuous treatment, dose reduced to 16 mg every two days
- Relationship ended, started drinking alcohol regularly, restarted using heroin
- Not taking buprenorphine regularly; put in mouth in front of pharmacist, left pharmacy and removed tablet; saved eleven 8 mg tabs
- Continued to use heroin, not taking buprenorphine
- Decided one day to take buprenorphine, reported taking 40 mg at once

Case Study #4

- Experienced withdrawal within one hour of ingestion
 - Agitation, nausea, sweating, abdominal cramps
- Attempted to alleviate withdrawal by taking more buprenorphine (24 mg) and had no relief
- Took another 16-24 mg of buprenorphine and continued to experience agitation, poor sleep, abdominal cramps, diarrhea, sweating
- Presented to clinic 2 days later, appeared restless and agitated, requested more buprenorphine
 - Was given buprenorphine 16 mg and continued to have opioid withdrawal
 - Used heroin that night, no relief
- Next day told staff what happened, transferred to methadone treatment and withdrawal symptoms resolved

Case Study #4

- Take-home points
 - Relative safety of buprenorphine in high doses (took 88 mg in one day), illustrates ceiling effect
 - Withdrawal symptoms typically start within 1-3 hours after buprenorphine and can last for days
 - Further doses of buprenorphine may not be helpful in relieving withdrawal

Case Study #5

- 62 year old man with OUD on methadone 165 mg daily
- Decided to change to buprenorphine due to prolonged QTc at current dose and insufficient relief of cravings at current dose
- Went to an inpatient unit to have methadone slowly tapered over days
- Received methadone 165 mg the day he was admitted
- The next day was prematurely administered buprenorphine 4 mg
- Developed opioid withdrawal, left AMA
- Returned to first provider, admitted to ICU to monitor severe opioid withdrawal
 - Anxiety, myalgia, flushing, lacrimation, chills, N/V/D, elevated BP, severe discomfort
- Decided to do rapid buprenorphine titration (increase by 8 mg per day) in ICU
- On day 4 received buprenorphine 32 mg; withdrawal was alleviated
- Discharged with follow-up

Methadone to Buprenorphine

- Reduce dose of methadone to 40 mg daily or less
- Hold methadone for 48 to 72 hours
- Start low dose buprenorphine (2 mg)

- Strategy employed in this case study #5 was to occupy opioid receptors as fully as possible to eliminate withdrawal
- Considered using methadone or fentanyl but decided against due to long QTc
- Considered clonidine but did not believe that would alleviate symptoms and cravings adequately

What about fentanyl?

- Qualitative study from 63 interviews from October 2018 to June 2019
- Aged 19-70 (mean age 38.9 years), most non-Hispanic White, 54% male
 - 1 subject stated he never used heroin or fentanyl
 - 3 subjects stated they never knowingly used fentanyl
- 85.7% had participated in buprenorphine treatment in past
- Nearly all subjects used non-prescribed buprenorphine (w/d or maintenance)
- Prevalence of fentanyl resulted in some people using nonprescribed buprenorphine and getting into treatment because of fear of overdose

What about fentanyl?

- Some who used buprenorphine developed precipitated withdrawal after waiting long periods, one participant waited 80 hours
- Participant started using kratom to treat initial withdrawal while waiting to take buprenorphine
- Some participants went to methadone treatment because buprenorphine not helpful
- Fentanyl is very lipophilic, high dose stays in body longer, high mu affinity
- Recommendation that need COWS >13 to start buprenorphine

Case Study #6

- 34 year old woman admitted to detox unit for opioid withdrawal
- No significant medical history
- Reported she was using 10 bags of heroin per day, last use day prior to admission
- Physical exam showed injection sites on bilateral arms, mild withdrawal (COWS=6)
- Urine tox was negative for opiates
- Was originally started on clonidine and she consented to buprenorphine taper
- Given dose of buprenorphine 2 mg
- Started having severe withdrawal within 1 hour of buprenorphine (restless, nausea, vomiting, writhing on the floor)
- Given another dose of buprenorphine 2 mg, stated she felt worse and refused any further doses
- Given IVF, antiemetic, clonidine, lorazepam
- Refused buprenorphine for rest of admission, took clonidine

Microdosing of buprenorphine to avoid withdrawal

- Methods developed to introduce buprenorphine into system without requiring a period of abstinence or the patient to be in withdrawal
- Four case series where patients cannot tolerate withdrawal psychologically or due to pain
- Kornfeld & Reetz (2015) started pain patients (no OUD) on transdermal buprenorphine while still receiving full opioid agonist for pain; full opioid agonist dose was reduced within 1 day; the following day given low dose sublingual buprenorphine and full agonist stopped

Microdosing of buprenorphine in OUD

- Canadian
 - Azar et al. (2018) used fentanyl patch to transition hospitalized patient from methadone to buprenorphine; patch worn one day, removed and then started low dose (1-2 mg) buprenorphine dosing every 2 hours to 8 mg; the following day received 8/2 mg which he stayed on
 - Klaire et al. (2019) used microdoses of buprenorphine while patient still receiving full agonist; two cases 3-5 days to get to full dose of buprenorphine
- Switzerland
 - Bernese method used microdoses of buprenorphine while patients continued use of full agonist and doses were tapered over time; two cases 9-30 days for transition (Hammig et al., 2016)

HOW TO TREAT PRECIPITATED WITHDRAWAL



Medications for Opioid Withdrawal

- Clonidine, Lofexidine
 - Alpha-2-adrenergic agonists
- Buprenorphine
 - Mu-opioid receptor partial agonist
- Methadone
 - Mu-opioid receptor full agonist

Alpha-2-Agonists

- Opioids are mu-receptor agonists, and inhibit cyclic AMP; when chronic opioids are discontinued, cyclic AMP system in noradrenergic system become overactive
- Alpha-2-agonists suppress noradrenergic hyperactivity in locus coeruleus associated with opioid withdrawal
 - Aches
 - Rhinorrhea
 - Lacrimation
 - Temperature dysregulation
 - Diaphoresis

Kosten & O'Connor, 2003



Dosing of Alpha-2-Agonists

- Clonidine
 - Off-label use since 1970s
 - 0.1 mg to 0.2 mg every 4 hours, up to 1.2 mg per day
 - Start tapering dose after day 3-4
 - Typically use for up to 10 days
 - Dosing may be limited by hypotension, bradycardia
 - Adverse effects of dry mouth, somnolence, fatigue

Dosing of Alpha-2-Agonists

- Lofexidine
 - FDA approval in 2018, used in Europe for years
 - Three 0.18 mg tabs 4 times daily
 - Dosing guided by symptoms
 - Total daily dosage should not exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets)
 - Gradual dose reduction (1 tab per dose) over 2-4 days
 - Indication for up to 14 days
 - Was shown to produce more rapid resolution in symptoms, less hypotension, and retain people longer than clonidine

Lofexidine

- Possible adverse effects & warnings
 - Hypotension, bradycardia, syncope
 - Somnolence
 - Dry mouth
 - QT prolongation
 - CNS depression when used with other CNS depressants
 - Increased risk of opioid overdose if resume using after withdrawal
- CYP2D6 inhibitors may increase plasma levels (e.g., paroxetine)
- Poor CYP2D6 metabolizers may have more adverse effects

Meds for Associated Symptoms

- Anxiety – Hydroxyzine Pamoate
- Diarrhea – Loperamide, sometimes may need to switch to Diphenoxylate/Atropine
 - Increase in self-treatment with loperamide – QT prolongation, TdP
- Nausea – ondansetron, other antiemetics
- Insomnia – Trazodone, Melatonin, Mirtazapine

Buprenorphine

- Mu-partial agonist
- High affinity for mu receptor, slow dissociation
- Usually combined with naloxone to prevent misuse of medication; do not recommend use of mono-product
- Pt needs to be in withdrawal to start medication, typically COWS ≥ 8 to prevent precipitated withdrawal
 - If develop precipitated withdrawal, suggested to repeat buprenorphine 2 mg every 1-2 hours
 - Use ancillary meds (clonidine, antiemetic, NSAIDs)

Buprenorphine vs. Clonidine

- Prospective, randomized, open-label study of buprenorphine and clonidine
- 344 men and women with OUD
- 13-day medically supervised withdrawal study
- Either inpatient or outpatient withdrawal setting
- Adjusting for level of care (IP vs OP), those who received buprenorphine were
 - nine times more likely to have achieved treatment success (attended appointment and negative urine tox) than those receiving clonidine (OR = 9.503, 95% CI: 4.604 – 19.614, $p < .001$)
 - 22 times more likely to complete treatment (OR = 22, 95% CI: 11 – 46 $p < .001$)
 - 69.1% receiving clonidine dropped out by day four versus 12% of patients receiving buprenorphine-naloxone, $\chi^2 (1, N = 344) = 115.765, p < .001$

Methadone

- Methadone is full mu-opioid agonist
- No need to have specific level of withdrawal to start, however, not wise to start when intoxicated
- Starting dose 20-30 mg, may need to increase slightly to alleviate withdrawal symptoms, then start decreasing the dose
- Reduction of 3% of dose vs. 10% of dose per week has higher retention, less withdrawal, less illicit opioid use
 - Only 40% achieve abstinence in either group
- Starting at methadone 35 mg daily and reducing over 21 days did not offer advantage in alleviating withdrawal or achieving abstinence compared to abrupt cessation and use of clonidine

Antagonist Assisted Withdrawal for Naltrexone-XR

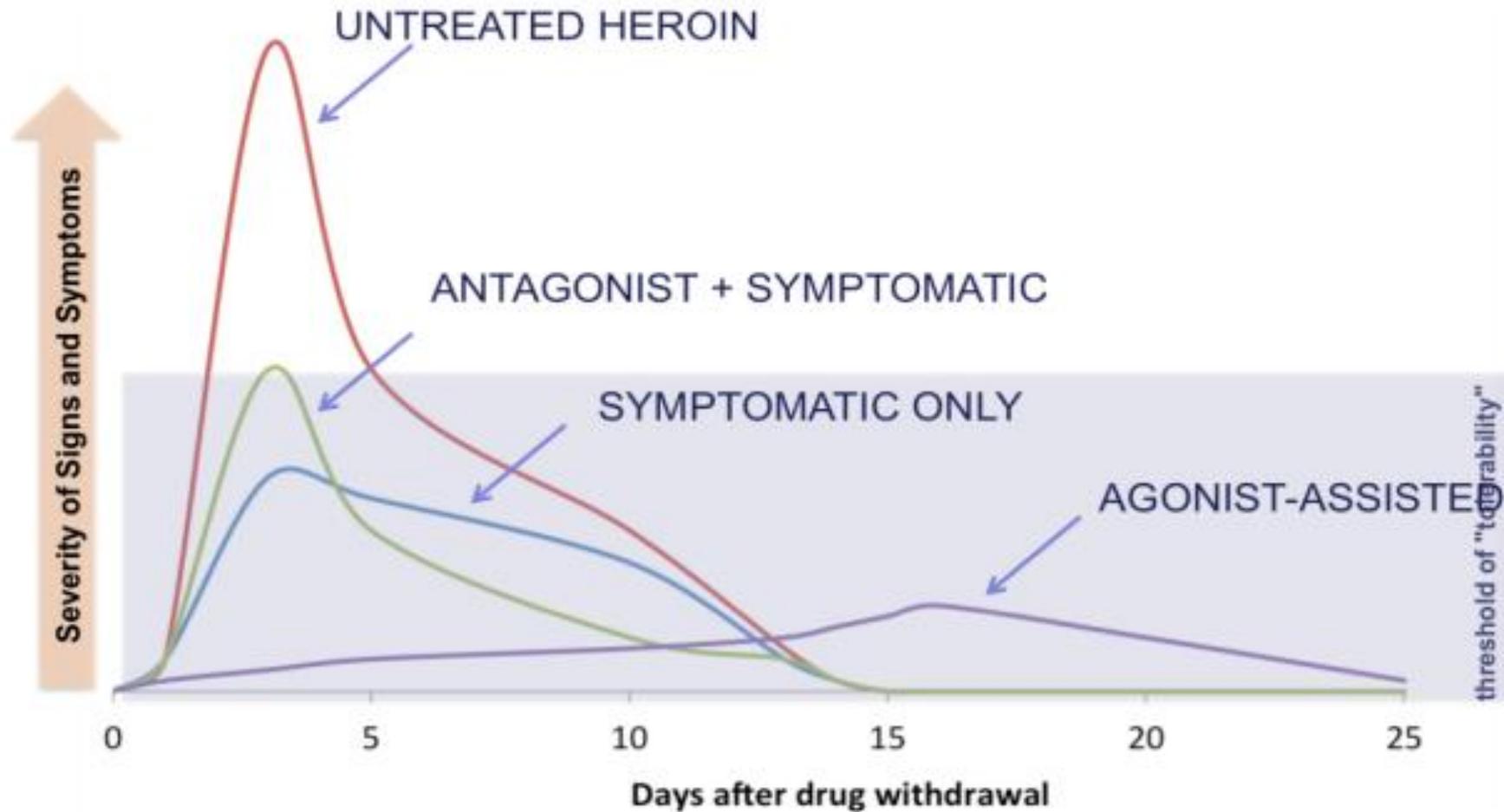
TABLE 1. Outpatient Opioid Detoxification Regimen, by Treatment Arm, in a Study of Oral Naltrexone Versus Buprenorphine as Detoxification Strategies for Extended-Release Injectable Naltrexone Induction in Opioid Dependence

Protocol Day	Naltrexone-Assisted Detoxification	Buprenorphine-Assisted Detoxification
1	Ancillary medications ^a to support abstinence	
2	Buprenorphine, 2 mg sublingually every 1–2 hours, up to 8 mg	
3	(Washout)	Buprenorphine, 6 mg
4	Naltrexone, 1 mg	Buprenorphine, 4 mg
5	Naltrexone, 3 mg	Buprenorphine, 4 mg
6	Naltrexone, 12 mg	Buprenorphine, 2 mg
7	Naltrexone, 25 mg	Buprenorphine, 1 mg
8	Extended-release injectable naltrexone, 380 mg i.m.	
15		Extended-release injectable naltrexone, 380 mg i.m.

^a Ancillary medications offered included clonidine (0.1 mg q.i.d., plus every 4 hours as needed; maximum daily dose, 1.2 mg), clonazepam (0.5 mg q.i.d.; maximum daily dose, 2.0 mg), prochlorperazine (10 mg t.i.d.), trazodone (100 mg h.s.), and zolpidem (10 mg h.s.).

- 150 participants randomized
- Open-label
- Participants with naltrexone-assisted detoxification were significantly more likely to
 - be successfully inducted to naltrexone-XR (56.1% compared with 32.7%)
 - receive the second naltrexone injection at week 5 (50% vs. 26.9%)

Severity of Withdrawal by Treatment



QUESTIONS/COMMENTS