Pain, Opioids and Buprenorphine: Mini Bootcamp

Disclosures

- **Planning Committee:** The speakers and members of the planning committee have nothing to disclose.

- Slides adapted from Dr. Robbins, Korthuis, and Gregg.

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Part 1: Pain, Opioids, and Opioid Failure

Learning Objectives

1. Employ universal precautions in opioid prescribing.
2. Define opioid success in primary care.
3. Detect opioid failure in primary care.
4. Screen for fibromyalgia in patients on opioids.
5. Use a risk-benefit ratio for opioid prescribing.

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https://dumielauxepices.net/wallpaper-2904364

HPI: 45 year-old woman new to my practice

Past medical: DM2 (last A1C 9.2), HTN, tobacco use

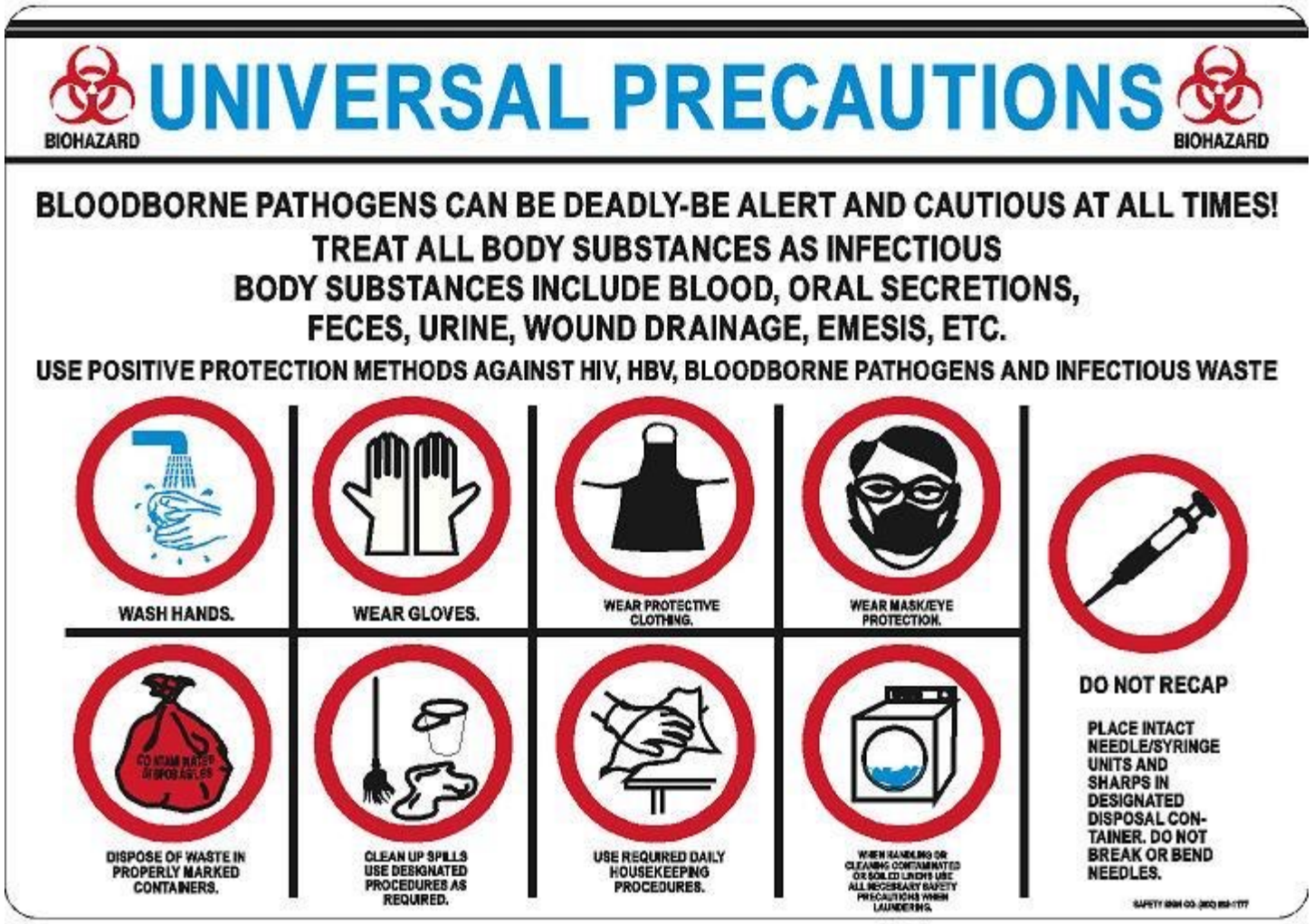
Psych: PTSD from abuse during first marriage

Pain generators: Diabetic neuropathy, chronic low back pain

Medications: oxycodone 5 mg 10/day, nortriptyline 10 mg QHS, statin, ASA, glargine insulin, metformin

MEDD: 75

Social: not working, one teenage boy, husband (2^{nd}) owner-operator of tractor trailer, no EtOH or other drugs



https://safetysignco.com/products/universal-precautions-sign

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"Universal Precautions"

(not evidence-based but has become "standard" of care)

Misuse risk assessment

- ORT - Opioid Risk Tool
- SOAPP - Screener and Opioid Assessment for Patients with Pain

Patient Provider Agreements (PPA)

- Informed consent (risks and benefits)
- Plan of care including medication management

Frequent face-to-face visits

- Assess and document risks and benefits

Monitor for adherence, addiction and diversion

- Urine drug monitoring and pill counts
- Prescription Drug Monitoring Program (PDMP) data

Gourlay DL et al. *Pain Med* 2005, slide courtesy Dan Alford.

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Opioid Success

Efficacy: improved function and quality of life

Safety: minimal current side-effects and minimal long-term risks

Alternatives: explored, optimized, and exhausted

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Busse JW et al. JAMA 2018.
Krebs EE et al. JAMA 2018.
Goldenberg DL Clauw DJ et al. Mayo Clin Proc 2016.

Opioid Safety and Risks

- **Allergies** are rare
- **Side effects** are common
  - Nausea, sedation, constipation, urinary retention, sweating
  - Respiratory depression – sleep apnea
- **Organ toxicities** are rare
  - Suppression of hypothalamic-pituitary-gonadal axis
- **Worsening pain** *(hyperalgesia in some patients)*
- **Addiction (Opioid use disorder)**
- **Overdose**
  - when combined w/ other sedatives
  - at high doses

Dunn KM et al. Ann Intern Med 2010
Li X et al. Brain Res Mol Brain Res 2001
Doverty M et al. Pain 2001
Angst MS, Clark JD. Anesthesiology 2006

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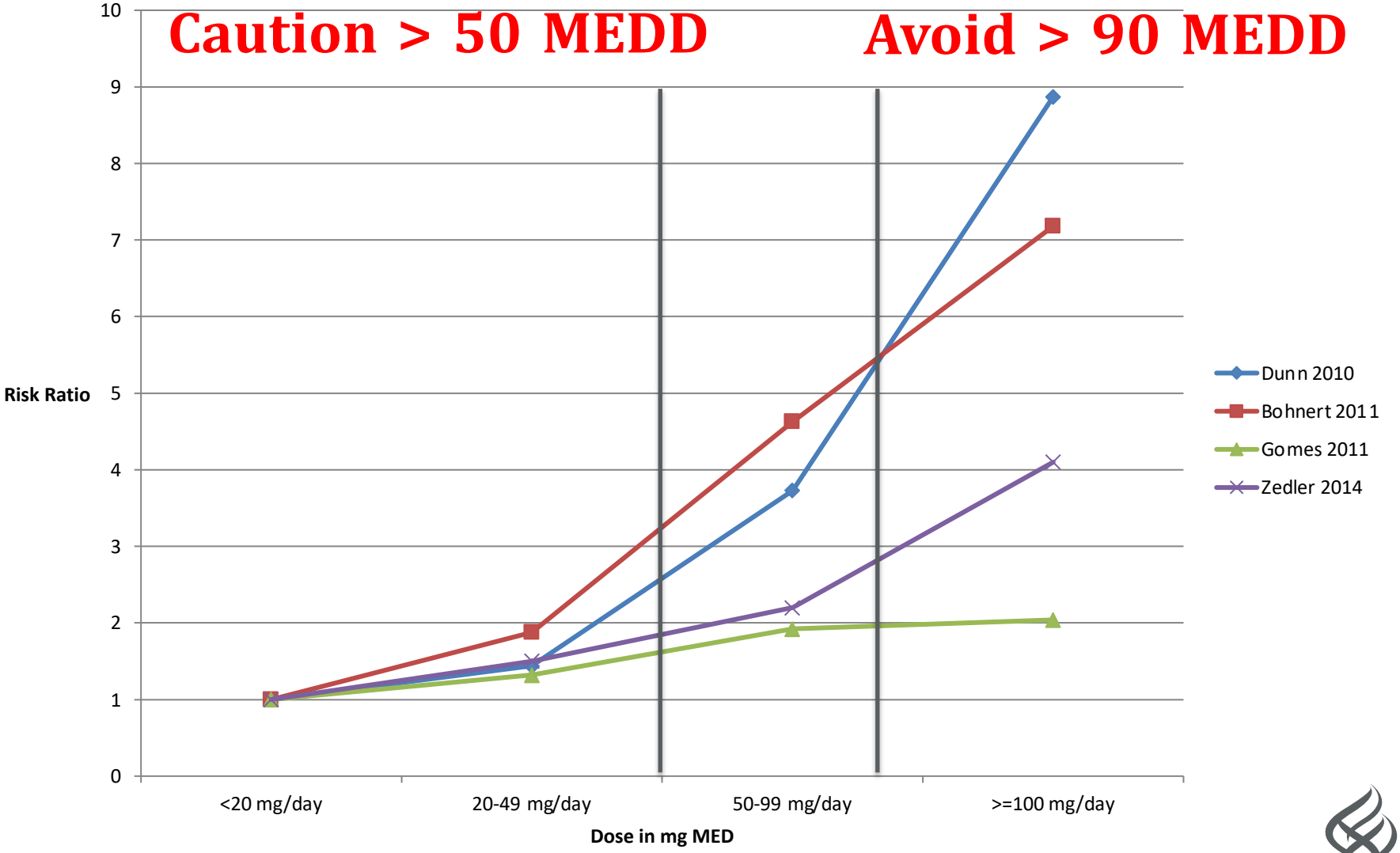
Dose-related Risk of Overdose



Courtesy Gary Franklin, Roger Chou

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URINE DRUG SCREEN (MULTIPLE-CLASS),POC

Order: 198069880

Collected: **4/30/2018 11:44** Status: **Final result** Visible to patient: **No (Not Released)** Dx: **Chronic pain syndrome ; Preventative ...**

	Ref Range & Units	Value
(THC) MARIJUANA, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
COCAINE, URINE	Negative	negatve
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
OPIATES, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
OXYCODONE, URINE	Negative	positive
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
AMPHETAMINES, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
METHAMPHETAMINES, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
METHADONE, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
BENZODIAZEPINES, URINE	Negative	negative
QC: ENTER 'PASS' OR 'FAIL', URINE DRUG SCREEN		pass
Resulting Agency		OHSU - MARQUAM HILL, POINT OF CARE TESTS

Specimen Collected: **04/30/18 11:44** Last Resulted: **04/30/18 11:46**

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Filled	ID	Written	Drug	QTY	Days
05/27/2017	1	05/26/2017	OXYCODONE HCL 5 MG TABLET	280	28
05/09/2017	1	05/01/2017	DIAZEPAM 10 MG TABLET	10	28
05/03/2017	1	05/01/2017	OXYCODONE HCL 5 MG TABLET	280	30
04/09/2017	1	04/03/2017	DIAZEPAM 10 MG TABLET	10	30
04/05/2017	1	04/03/2017	OXYCODONE HCL 5 MG TABLET	280	28
02/08/2017	1	02/08/2017	OXYCODONE HCL 5 MG TABLET	280	30
02/08/2017	1	02/08/2017	DIAZEPAM 10 MG TABLET	10	30
01/13/2017	1	01/13/2017	OXYCODONE HCL 5 MG TABLET	280	30
01/13/2017	1	01/13/2017	DIAZEPAM 10 MG TABLET	10	30
11/18/2016	1	11/17/2016	OXYCODONE HCL 5 MG TABLET	280	28
11/14/2016	1	11/14/2016	DIAZEPAM 10 MG TABLET	10	30
10/21/2016	1	10/21/2016	OXYCODONE HCL 5 MG TABLET	280	28
10/18/2016	1	10/18/2016	DIAZEPAM 10 MG TABLET	10	30
09/23/2016	1	09/20/2016	OXYCODONE HCL 5 MG TABLET	280	28
08/26/2016	1	08/24/2016	OXYCODONE HCL 5 MG TABLET	280	28
08/19/2016	1	08/19/2016	DIAZEPAM 10 MG TABLET	10	30
07/29/2016	1	07/29/2016	OXYCODONE HCL 5 MG TABLET	280	28
07/22/2016	1	07/22/2016	DIAZEPAM 10 MG TABLET	10	28
07/01/2016	1	07/01/2016	OXYCODONE HCL 5 MG TABLET	280	28
06/24/2016	1	06/24/2016	DIAZEPAM 10 MG TABLET	10	30
06/04/2016	1	05/19/2016	OXYCODONE HCL 5 MG TABLET	280	28
06/03/2016	1	06/03/2016	HYDROCODON-ACETAMINOPHEN 5-325	16	2
05/26/2016	1	05/26/2016	DIAZEPAM 10 MG TABLET	10	30
05/07/2016	1	05/07/2016	OXYCODONE HCL 5 MG TABLET	280	28
04/26/2016	1	04/18/2016	DIAZEPAM 10 MG TABLET	10	30

Patient-Provider Agreement

http://www.theolivebranchblog.com/wp-content/uploads/2013/07/agreement.png

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Internal Medicine

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CHRONIC OPIOID TREATMENT INFORMED CONSENT AND NOTICE OF MATERIAL RISKS

Page 1 of 1

ACCOUNT NO.
MED. REC. NO.
NAME
BIRTHDATE

Patient Identification

You have been diagnosed with this condition: diabetic nerve pain, low back pain

I have recommended long-term treatment with the following opioid medicine(s): Oxycodone 5mg

It is realistic to expect a reduction of pain during short-term use of opioid medication. However, opioids do not always improve pain or function with long-term use, and complete relief of pain is unlikely. Improved function should be your primary goal from opioid treatment.

Goal(s) for improvement in function: go back to work, do basic house work, walk around block.

Alternatives to opioid medicine that could improve your pain include:

- ☐ nonsteroidal anti-inflammatory drugs (NSAIDs)
- ☒ acetaminophen (Tylenol®)
- ☒ antidepressants
- ☒ neuropathic (nerve) pain medicines
- ☐ steroids (oral or injected)
- ☐ disease-specific drug treatments
- ☐ partial opioid (buprenorphine)
- ☐ muscle relaxants
- ☒ topical therapies
- ☐ nerve block
- ☐ surgery
- ☐ other: _____

Additional (non-drug) therapies that may be necessary for you to reach your goal(s) include:

- ☒ physical therapy
- ☒ exercise
- ☒ weight loss
- ☐ counseling/mental health visits
- ☒ pain psychology/support groups
- ☒ acupuncture
- ☒ massage
- ☒ meditation / mindfulness
- ☐ brace or splint
- ☒ other: water therapy

Long-term opioid use may be associated with the following risks

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Two-Month Follow-Up

http://girlgonetravel.com/wp-content/uploads/2012/01/calendar.jpg

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Assessing Benefit: PEG scale

1. What number best describes your pain on average in the past week:

0 1 2 3 4 5 6 7 8 **9** 10

No pain — Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 **8** 9 10

Does not interfere — Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 **9** 10

Does not interfere — Completely interferes

Krebs EE, et al. J Gen Intern Med. 2009

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http://www.reclinercity.com/kns54-rd-os.html

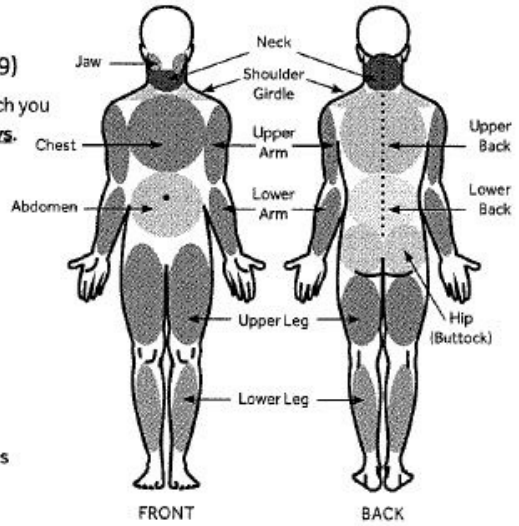
Widespread Pain Index (WPI)

(1 point per check box; score range: 1–19)

Please check the boxes below for each area in which you have had pain or tenderness **during the past 7 days**.

- [ ] Shoulder girdle, left
- [ ] Shoulder girdle, right
- [ ] Upper arm, left
- [ ] Upper arm, right
- [x] Lower arm, left
- [x] Lower arm, right
- [ ] Hip (buttock) left
- [ ] Hip (buttock) right
- [ ] Upper leg left
- [ ] Upper leg right
- [x] Lower leg left
- [x] Lower leg right
- [x] Jaw left
- [ ] Jaw right
- [ ] Chest
- [x] Abdomen
- [x] Neck
- [x] Upper back
- [x] Lower back
- [ ] None of these areas

WPI score: 9



Symptom Severity (score range: 1–12)

For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	[ ]	[ ]	[ ]	[x]
B. Trougle thinking or remembering	[ ]	[ ]	[ ]	[x]
C. Waking up tired (unrefreshed	[ ]	[ ]	[ ]	[x]

During the **past 6 months** have you had any of the following symptoms?

	Points	0	1
A. Pain or cramps in lower abdomen		[ ] No	[x] Yes
B. Depression		[x] No	[ ] Yes
C. Headache		[ ] No	[x] Yes

SS score: 11

Additional criteria (no score)

Have the symptoms listed on this sheet, and widespread pain been present at a similar level for **at least 3 months**?

[ ] No [x] Yes

TOTAL score: 20

OREGON PAIN GUIDANCE (OPG) OF SOUTHERN OREGON www.oregonpainguidance.org

Goldenberg, Clauw et al in Mayo Clinic Proc 2016

https://professional.oregonpainguidance.org/wp-content/uploads/sites/2/2017/05/Fibromyalgia_Screening_Tool.pdf

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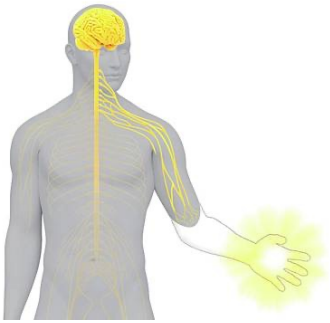


Central sensitization
(fibromyalgia)

Nociceptive ischemic/
inflammatory

Motor/autonomic

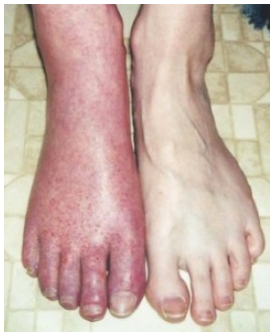
Mechanical
influence

Continuum of Pain Mechanisms

Nervous system
influence

Peripheral neurogenic

Affective
central



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Continuation of Opioids

- Before writing the next prescription…you should be convinced that…
  - …there is benefit (function, QOL, pain)
  - …benefits outweigh observed harms/risks

Slide courtesy Dan Alford

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Conclusions

1. Use universal precautions in opioid prescribing to detect opioid failure and to keep patients safe.
2. Screening tools such as the PEG-3, a risk stratification tool, and the WPI/SSS can help predict/detect opioid failure.
3. Fibromyalgia is not an opioid responsive pain condition.
4. Use a non-judgmental risk-benefit ratio for opioid prescribing.

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Part 2: Buprenorphine Basics

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Learning objectives

1. Understand the pharmacology of buprenorphine.
2. Implement standard and microdose buprenorphine induction.
3. Integrate buprenorphine into your existing primary care practice.

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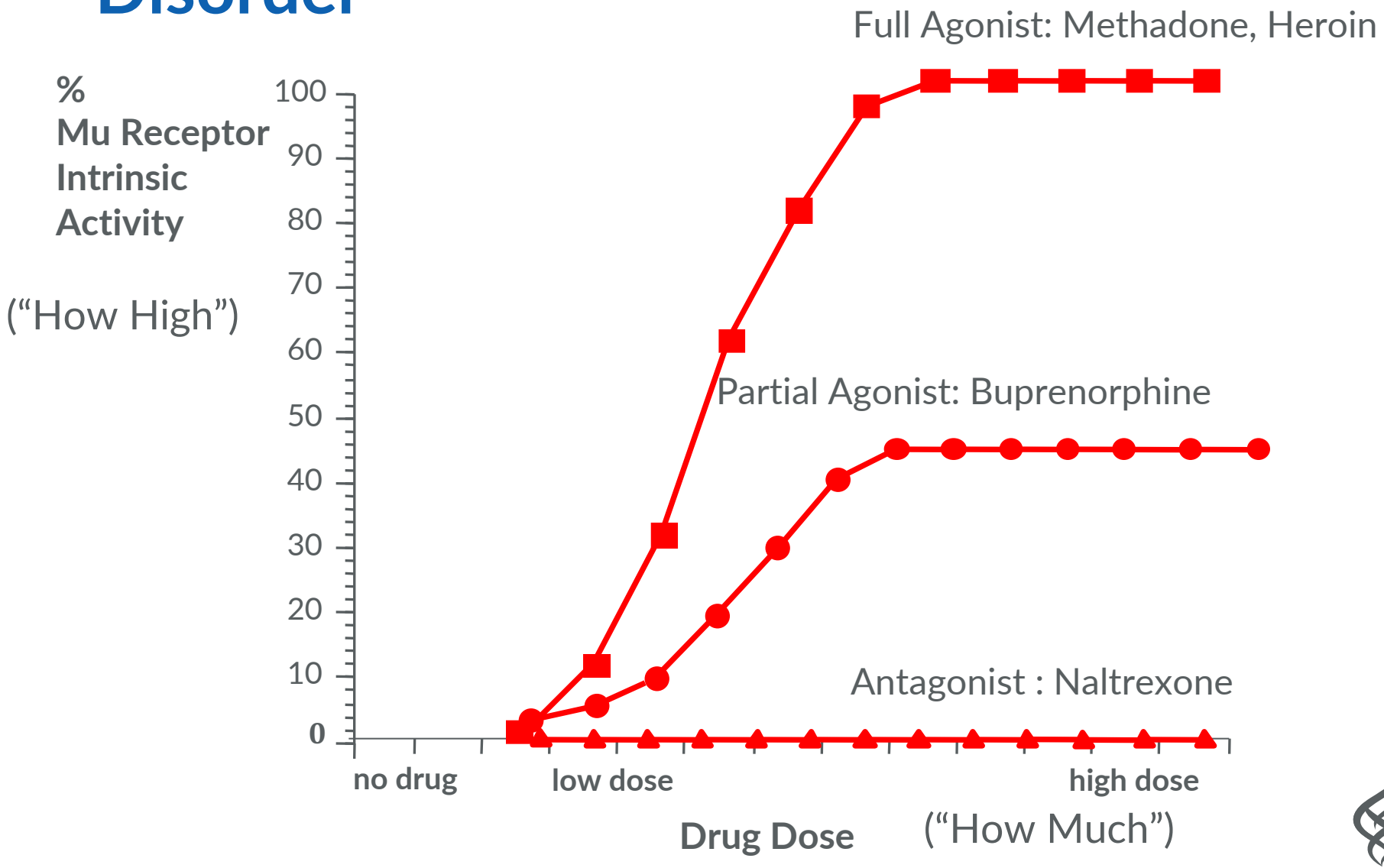
Pharmacotherapy for Opioid Use Disorder



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Buprenorphine/naloxone
(4:1 combination)

- Partial opioid agonist
  - Decreased overdose risk
- Naloxone inactive unless injected –then precipitates withdrawal
  - Decreased abuse risk
- Sublingual, once daily
  - Safe for flexible dosing

2mg/0.5mg

8mg/2mg

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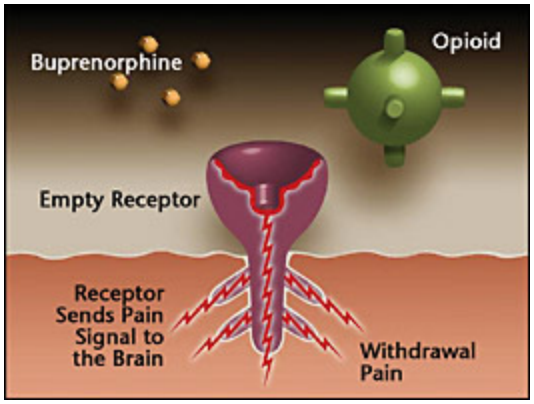
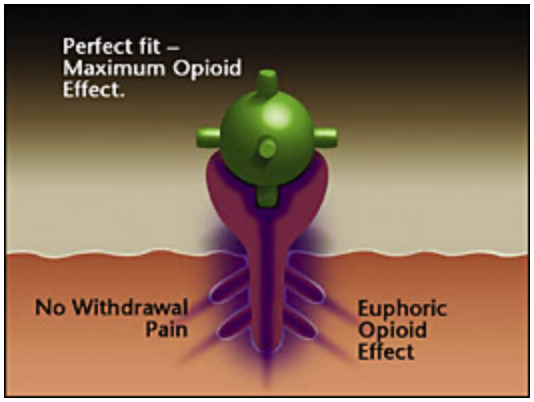
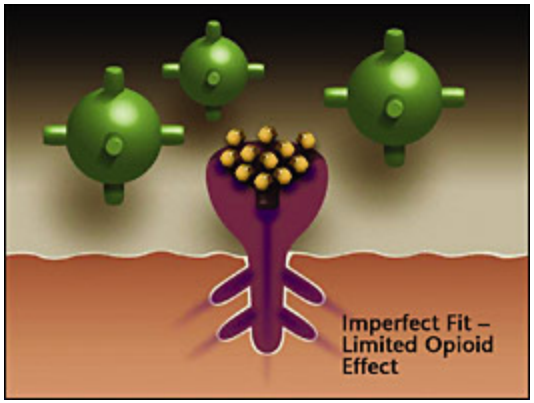
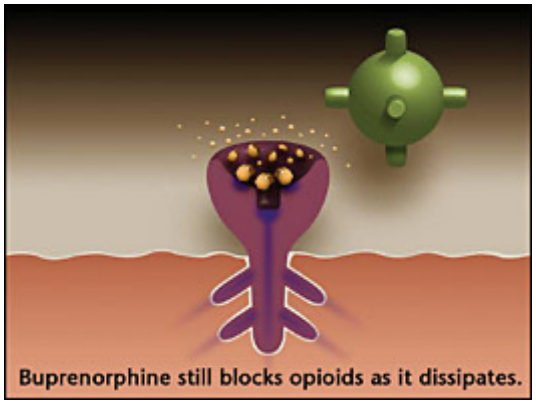
How Does Buprenorphine Work?









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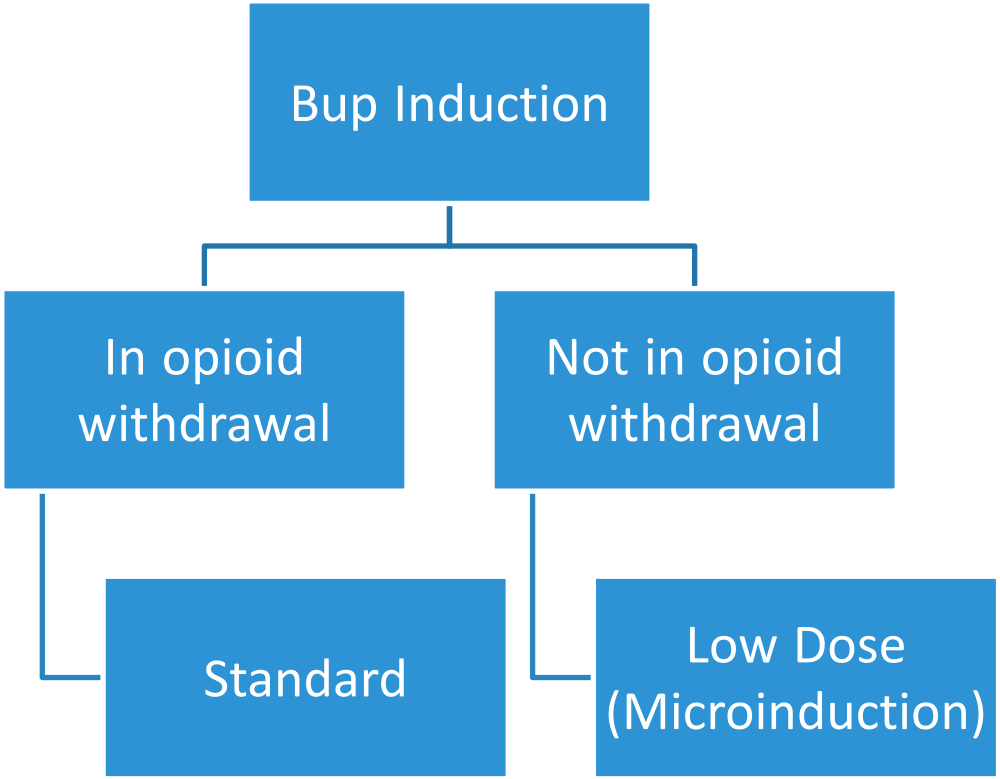
Buprenorphine Inductions



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Prior to Induction

- Counsel patient on
  - Alternative treatments
  - Induction timing
  - Precipitated withdrawal
  - Need for behavioral treatment
- Treatment agreement
- Labs:
  - UDS, HIV, HCV, HBV, HCG, liver enzymes
- Write prescription

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Timing of Buprenorphine Induction

- Schedule patient for induction soon after intake visit
- Must be in at least mild-to-moderate opioid withdrawal in order to begin induction
  - The more severe the withdrawal, the greater the relief
- Withdrawal symptoms typically begin
  - 12-24 hours after last dose of a short-acting opioids like heroin
  - 2-4 days after last dose of long acting opioids like methadone

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Clinical Opioid Withdrawal Scale (COWS)

Rates 11 Withdrawal Symptoms:

- Resting pulse rate
- Sweating
- Restlessness
- Pupil size
- Bone or joint aches
- Runny nose
- GI upset
- Tremor
- Yawning
- Anxiety or irritability
- Goose bumps

- Guides timing of first dose of buprenorphine

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Criteria for Giving First Dose Buprenorphine

- COWS ≥ 12, *or*…
- COWS < 12, *and* no self-reported opioid use in the past 3 day *and* clinical UDS negative for opioids

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Induction & Stabilization Dosing Schedule

Tailor to Patient

	Suggested Dosing*	Maximum Dose
Day 1	2-4mg (wait 45 min) + 4mg if needed	8-12mg
Day 2	Day 1 dose + 4mg if needed (single dose)	12-16mg
Day 3	Day 2 dose + 4mg if needed (single dose)	16mg
Day 3-28	May increase dose 4mg per week, if needed (single dose)	24mg

SAMHSA, *Medications for Opioid Use Disorder.* Treatment Improvement Protocol (TIP) Series 63; 2018. Available at https://store.samhsa.gov/product/SMA18-5063FULLDOC

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Home Induction

- Office-based induction can be a barrier to initiation
- Pilot trials of home vs. office-based inductions demonstrate comparable retention rates and safety
- Patient selection:
  - Understands induction process
    - Prior bup experience predicts success
  - Can contact provider for problems
- Provider available for phone consultation

Lee, JD, JAM 201
SAMHSA, TIP-63

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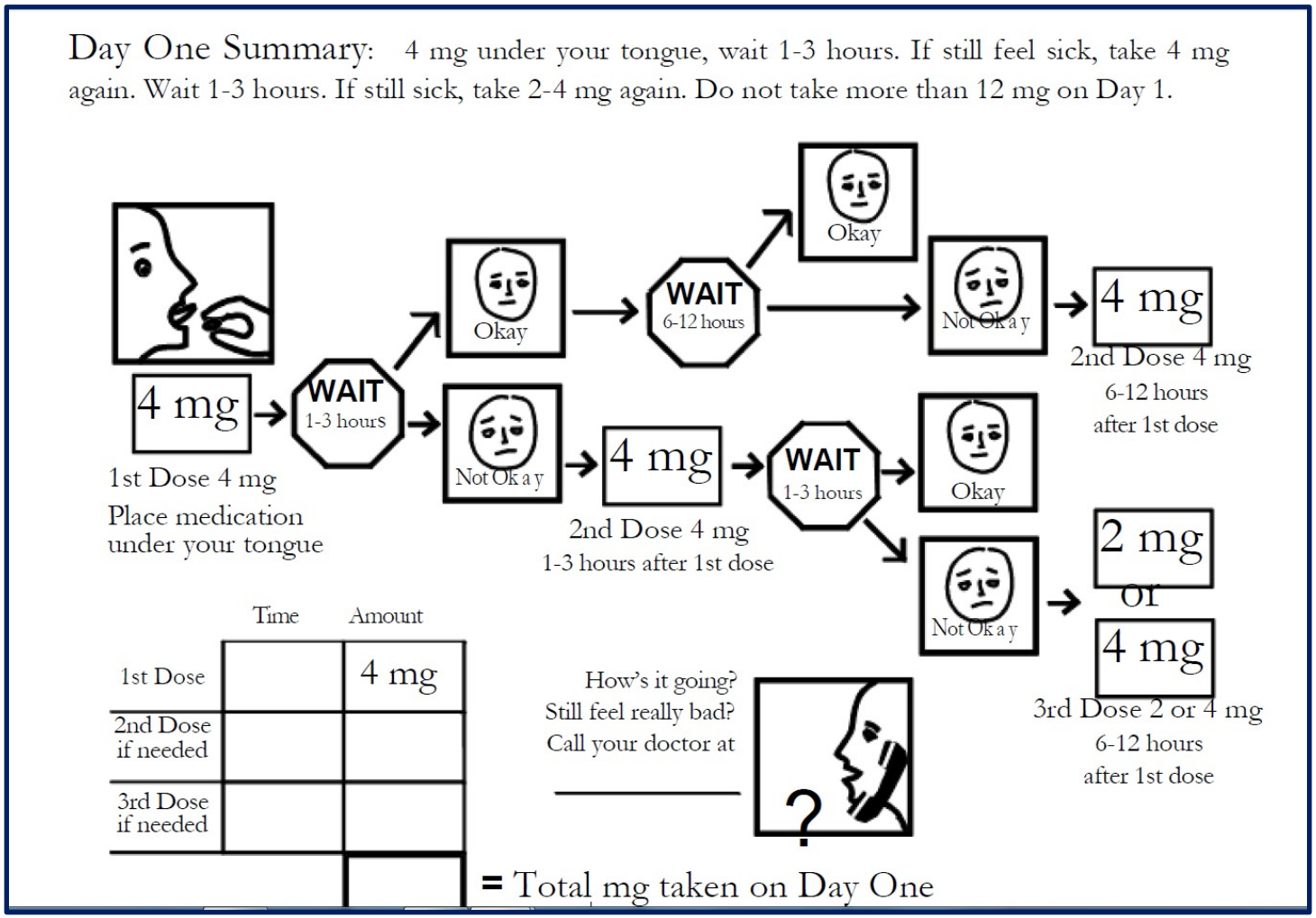
Home Induction Hand-Out



Lee, J. D., Vocci, F., & Fiellin, D. A. (2014). *Journal of Addiction Medicine, 8*(5), 299–308.

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Typical Buprenorphine Clinic Schedule

	Before Induction	Induction (Days 1-3)	Month 1	Month 2	Month 3 and after
Prior auth	X				
Treatment Agreement	X				
Clinic Visit	X	2x/week	Weekly	Every 2 weeks	Every 4 weeks
Counseling	X		Weekly	Every 2 weeks	Every 4 weeks
Prescription	+/-	1-3 day supply	7 day supply	14 day supply	28 day supply
UDS	X	X	weekly	every 2 weeks	monthly
Labs	X (HIV, HCV, HBV, urine HCG)				
PDMP	X (then with refills at least monthly)				

- Very stable patients often require less frequent visits & UDS
- Relapse reverts to Month 1 schedule until stable again

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Fentanyl

BRIEF REPORTS

Evidence of Buprenorphine-precipitated Withdrawal in Persons Who Use Fentanyl

Varshneya, Neil B. PhD; Thakrar, Ashish P. MD; Hobelmann, J. Gregory MD; Dunn, Kelly E. PhD, MBA; Huhn, Andrew S. PhD, MBA

Author Information

Journal of Addiction Medicine: 7/8 2022 - Volume 16 - Issue 4 - p e265-e268

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Fentanyl

Opioid Use Disorder Treatment in the Fentanyl Era

To the Editor:

The letter by Hartley et al.[1] describes a novel approach for buprenorphine initiation in an inpatient withdrawal management setting for persons who use fentanyl and were thought to be at risk of buprenorphine-precipitated withdrawal.

Conventional (ie, standard protocol) buprenorphine initiation involves administering 2–4 mg sublingual buprenorphine to patients with objective signs of withdrawal, followed by additional doses of 2–8 mg sublingual buprenorphine after 60–90 minutes if the first dose is well tolerated,[2] a strategy largely successful for individuals using heroin or prescription opioids. However, the illicit opioid supply in many parts of North America has been adulterated with or replaced by fentanyl and its analogs.[3] Recent evidence demonstrates that fentanyl use increases the risks of precipitated withdrawal when using a standard buprenorphine initiation approach,[4–6] but significant gaps still exist in the clinical and mechanistic understanding of this phenomenon. What is the actual incidence of precipitated withdrawal and, among individuals using fentanyl, what are the risk factors for precipitated withdrawal? Is precipitated withdrawal with traditional initiation due to fentanyl's lipophilicity, which leads to protracted and highly variable renal clearance among individuals with fentanyl use and dependence,[7] or due to another mechanism, such as mu-opioid receptor desensitization or reduced receptor availability? It is imperative we answer these empirical questions through both clinical research and animal models.

Last, and most importantly, what are the optimal strategies for buprenorphine initiation for individuals with fentanyl use disorder? The past 3 years has seen a flood of case series and reviews of approaches using low-dose initiation.[8–15] Hartley et al add to this literature with an approach that could be used in inpatient withdrawal management settings where full-agonist opioids are unavailable. They protocolized a 48-hour buprenorphine induction during a 3-month proof of concept pilot study that, to date, has successfully initiated more than 50 patients who reported using either primarily or exclusively fentanyl. The method used low doses of buprenorphine (1 mg sublingual) administered immediately upon admission, before the development of significant withdrawal symptoms, and continued for 24 hours, before starting maintenance buprenorphine doses (up to 20 mg sublingual within the first hour) on the second day. Hartley et al describe that this is a "low-to-high dose" approach; however, it should be noted that the traditional initiation process outlined by the American Society of Addiction Medicine guidelines also reaches maintenance doses of 16–24 mg sublingual daily by the second day.[2]

The United States is amid a historic overdose epidemic, a public health crisis driven by fentanyl and its analogs; during this time, patients deserve equitable, high-quality, and evidence-based care. Innovative research on patient centric interventions to address the fentanyl phenomenon and its effects on opioid use disorder (OUD) treatment is greatly needed. Proof of concept studies such as those of Hartley et al, which are uncontrolled and retrospective, are among the initial steps to develop appropriately informed patient and clinical practice evidence in this space. We additionally need prospective controlled studies that include both traditional outcomes such as overdoses, initiation rates, and retention in care for OUD as well as patient-reported outcomes such as treatment goals and satisfaction.[16]

Further research is also needed to examine fentanyl's unique pharmacokinetics in individuals with OUD and to understand the mechanisms underlying buprenorphine-precipitated withdrawal and fentanyl dependence.

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3. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. *Curr Opin Psychiatry.* 2021; 34(4):344–350.
4. Varshneya NB, Thakrar AP, Hobelmann JG, et al. Evidence of buprenorphine-precipitated withdrawal in persons who use fentanyl. *J Addict Med.* 2021. doi:10.1097/ADM.0000000000000922.

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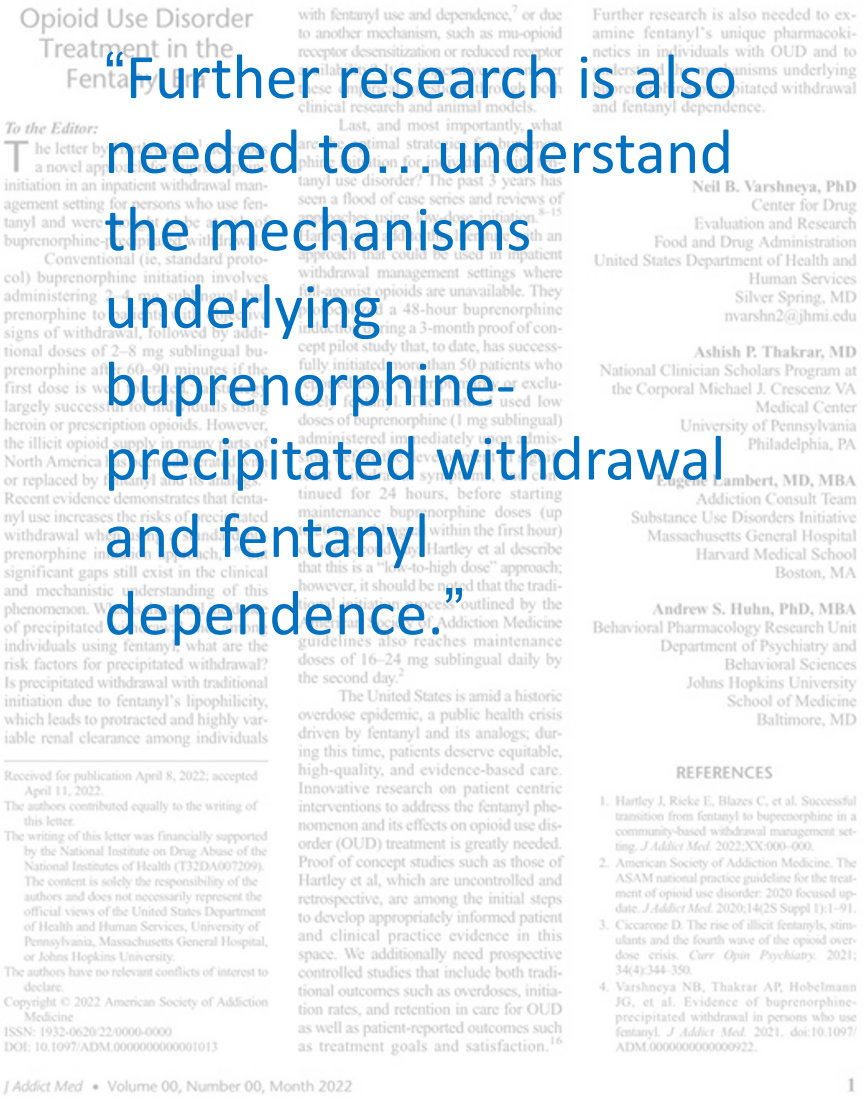
Fentanyl



LETTER TO THE EDITOR

Opioid Use Disorder Treatment in the Fentanyl Era

To the Editor:

The letter by ... a novel approach ... initiation in an inpatient withdrawal management setting for persons who use fentanyl and were ... buprenorphine-precipitated withdrawal.

Conventional (ie, standard protocol) buprenorphine initiation involves administering 2–4 mg sublingual buprenorphine to ... signs of withdrawal, followed by additional doses of 2–8 mg sublingual buprenorphine after 60–90 minutes if the first dose is well ... largely successful for individuals using heroin or prescription opioids. However, the illicit opioid supply in many parts of North America ... or replaced by fentanyl and its analogs. Recent evidence demonstrates that fentanyl use increases the risks of precipitated withdrawal when ... prenorphine initiation, ... significant gaps still exist in the clinical and mechanistic understanding of this phenomenon. ... of precipitated withdrawal? For individuals using fentanyl, what are the risk factors for precipitated withdrawal? Is precipitated withdrawal with traditional initiation due to fentanyl's lipophilicity, which leads to protracted and highly variable renal clearance among individuals with fentanyl use and dependence,[7] or due to another mechanism, such as mu-opioid receptor desensitization or reduced receptor ... clinical research and animal models.

Last, and most importantly, what ... animal strategies ... phine-precipitated ... tanyl use disorder? The past 3 years has seen a flood of case series and reviews of ... [8–15] ... approach that could be used in inpatient withdrawal management settings where ... ll-agonist opioids are unavailable. They ... a 48-hour buprenorphine ... ing a 3-month proof of concept pilot study that, to date, has successfully initiated ... than 50 patients who ... exclu- ... used low doses of buprenorphine (1 mg sublingual) administered ... mediately ... Finis- ... synthesis ... tinued for 24 hours, before starting maintenance buprenorphine doses (up ... within the first hour) ... Hartley et al describe that this is a "low-to-high dose" approach; however, it should be noted that the traditional initiation process outlined by the ... Addiction Medicine guidelines also reaches maintenance doses of 16–24 mg sublingual daily by the second day.[2]

The United States is amid a historic overdose epidemic, a public health crisis driven by fentanyl and its analogs; during this time, patients deserve equitable, high-quality, and evidence-based care. Innovative research on patient centric interventions to address the fentanyl phenomenon and its effects on opioid use disorder (OUD) treatment is greatly needed. Proof of concept studies such as those of Hartley et al, which are uncontrolled and retrospective, are among the initial steps to develop appropriately informed patient and clinical practice evidence in this space. We additionally need prospective controlled studies that include both traditional outcomes such as overdoses, initiation rates, and retention in care for OUD as well as patient-reported outcomes such as treatment goals and satisfaction.[16]

Further research is also needed to examine fentanyl's unique pharmacokinetics in individuals with OUD and to ... derstand ... anisms underlying ... itated withdrawal and fentanyl dependence.

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"Further research is also needed to…understand the mechanisms underlying buprenorphine-precipitated withdrawal and fentanyl dependence."

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Alternative Practice: Microinduction

- Low-dose initiation of bup while still on opioids
- Example:
    - Day 1: 0.5 mg (1/4 of a 2 mg tab)
    - Day 2: 0.5 mg BID
    - Day 3: 1 mg BID (1/2 tabs)
    - Day 4: 2 mg BID
    - Day 5: 4 mg BID
    - Stop or taper full agonists

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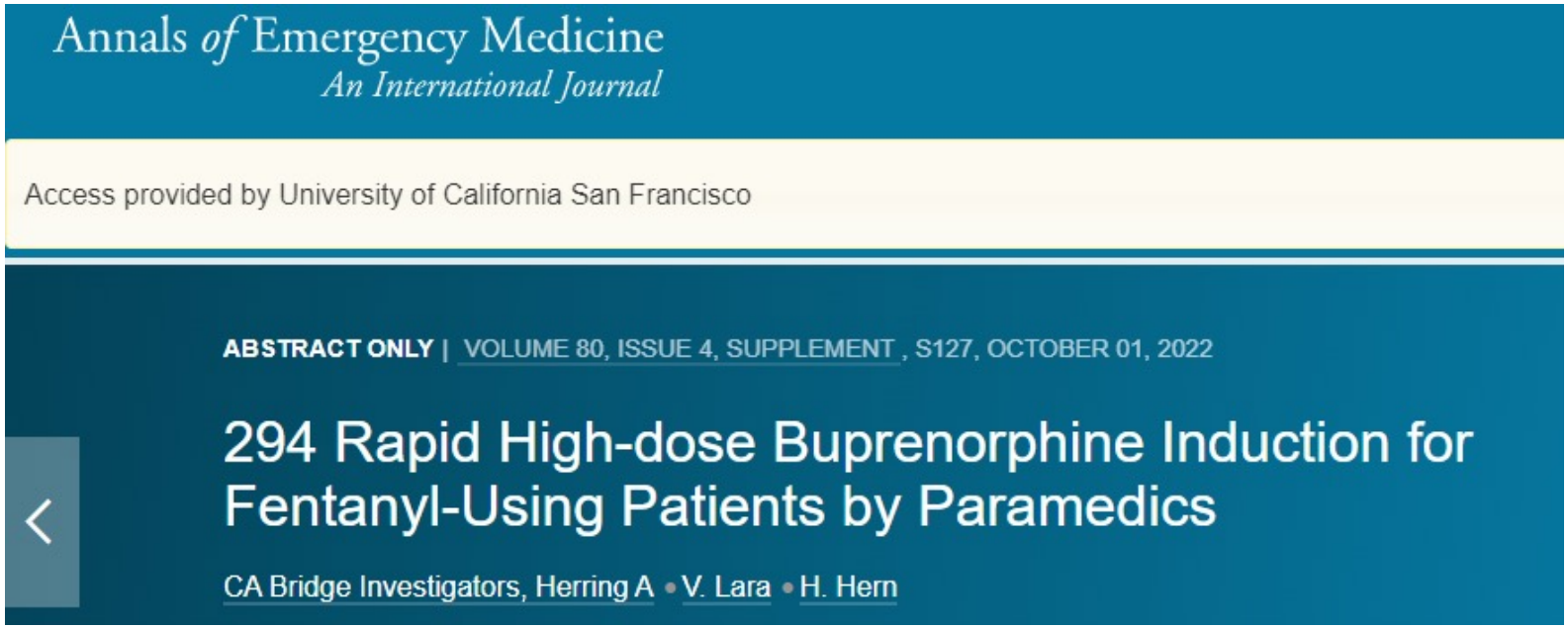
Alternative Practice: Microinduction

- Problem: it takes forever.

Alternative Practice: Rapid Induction



Annals *of* Emergency Medicine
An International Journal

ABSTRACT ONLY | VOLUME 80, ISSUE 4, SUPPLEMENT , S127, OCTOBER 01, 2022

294 Rapid High-dose Buprenorphine Induction for Fentanyl-Using Patients by Paramedics

CA Bridge Investigators, Herring A • V. Lara • H. Hern

Starting dose of 16-24 mg!

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Alternative Practice: Rapid Induction

- Problem: people can still get precipitated withdrawal.

Alternative Practice: Rapid Induction

- Problem: people can still get precipitated withdrawal, sometimes up to 48 hours later, and unpredictably!

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Alternative Practice: Low Dose-High Dose?

LETTER TO THE EDITOR

Successful Transition from Fentanyl to Buprenorphine in a Community-based Withdrawal Management Setting

Hartley, Jennifer PhD, MD; Rieke, Eowyn MD, MPH; Blazes, Christopher MD; Smith, Benjamin MD, MPH; Gregg, Jessica PhD, MD

Author Information

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What do we do?

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Part 3: Medications for Opioid Use Disorder

Who should get what when?

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Objectives

Compare methadone, buprenorphine, ER buprenorphine, ER naltrexone in terms of:

1. Efficacy (on a stable dose)
2. Induction and other clinical variables

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Methadone: efficacy

Cochrane review 2009

- methadone v treatment without medication
- Patients on methadone significantly less likely to have positive urine drug screen
- Decreased new infections with Hep C/HIV
- Decreased criminality

Mattick RP, et al. *Cochrane Database of Systematic Reviews* 2009

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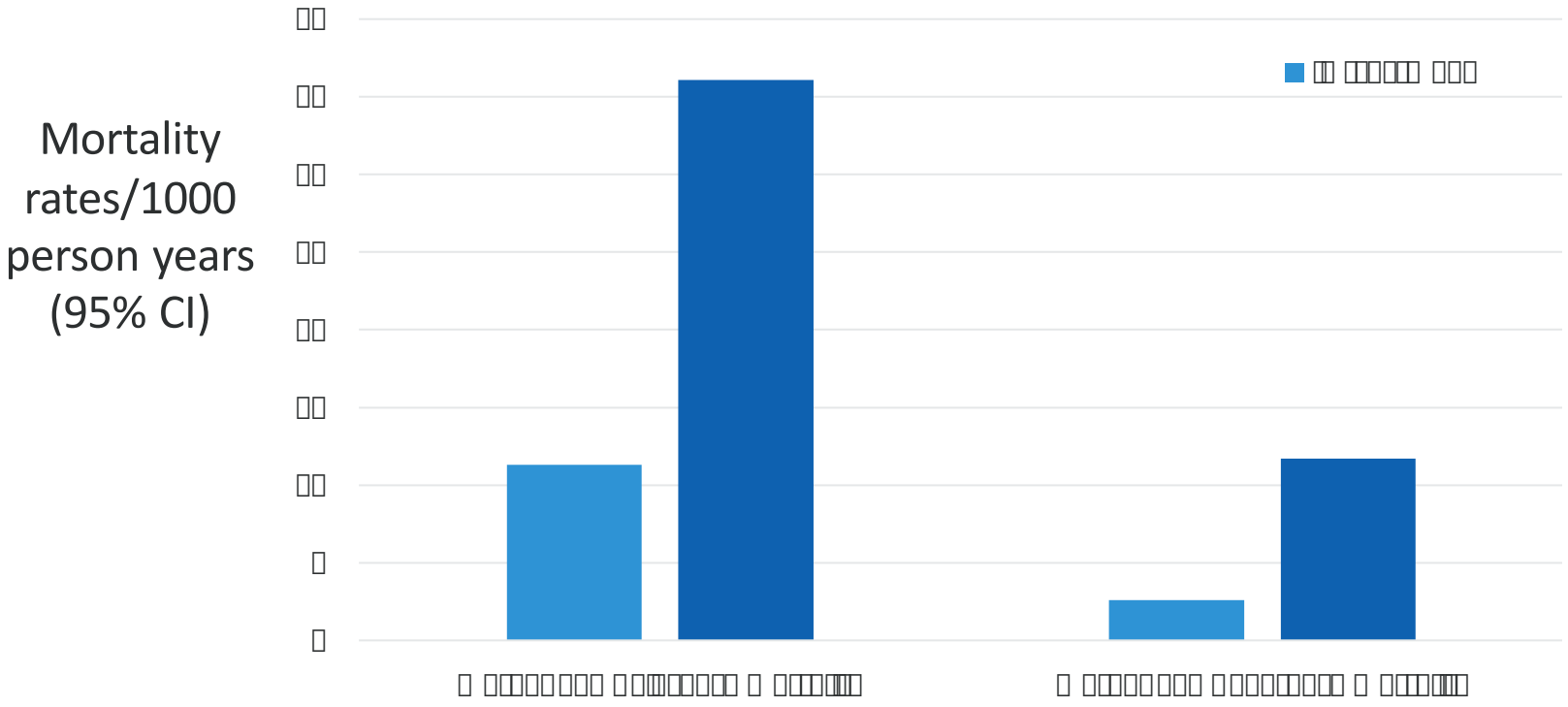
Mortality Risk during and after methadone treatment



Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

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Buprenorphine: efficacy

Cochrane review 2014

- low dose, medium dose, high dose
- Buprenorphine was equivalent to methadone for suppression of illicit drug use except at very low doses
- No difference in mortality

Mattick RP, et al. *Cochrane Database of Systematic Reviews* 2014.

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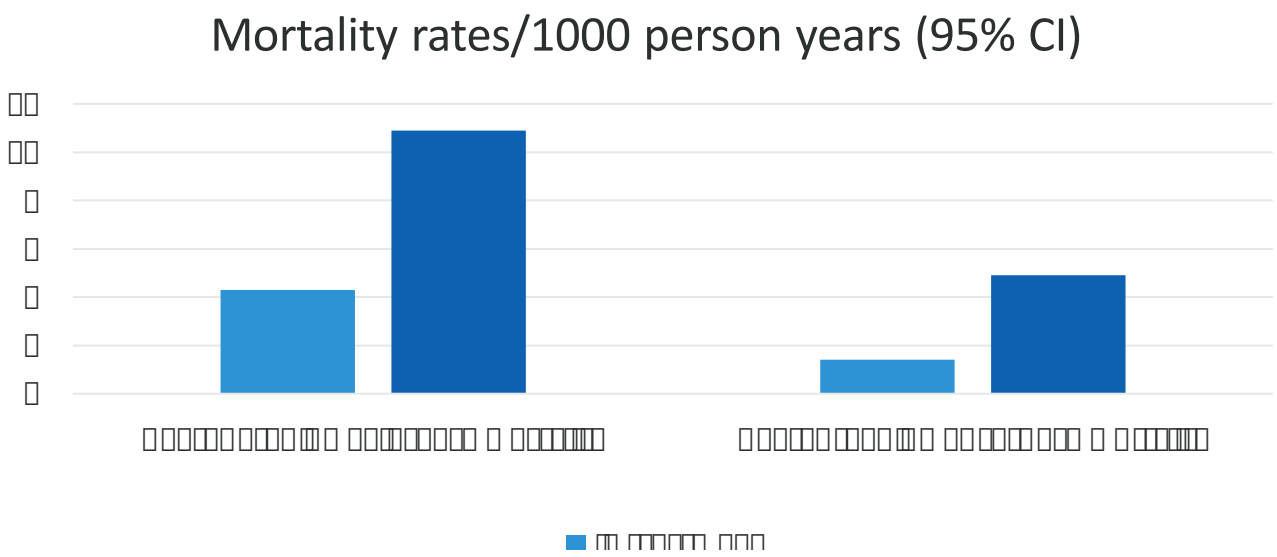
Mortality Risk during and after buprenorphine treatment



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New kid in town: buprenorphine XR

2019 randomized control trial compared three groups over 6 months:

- Six injections of 300mg
- Two injections of 300mg then four of 100mg
- Placebo injections

Results:

- Mean abstinence: 41% for 300mg group;
- 42.7% for 300/100mg group
- 5% for placebo

Haight et al The Lancet 2019

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New kid in town:buprenorphine XR

Patient Centered Outcomes

- Improved physical and mental health measures
- Increased employment
- Increased medication satisfaction
- Decreased health care utilization

Ling et al JAM 2019

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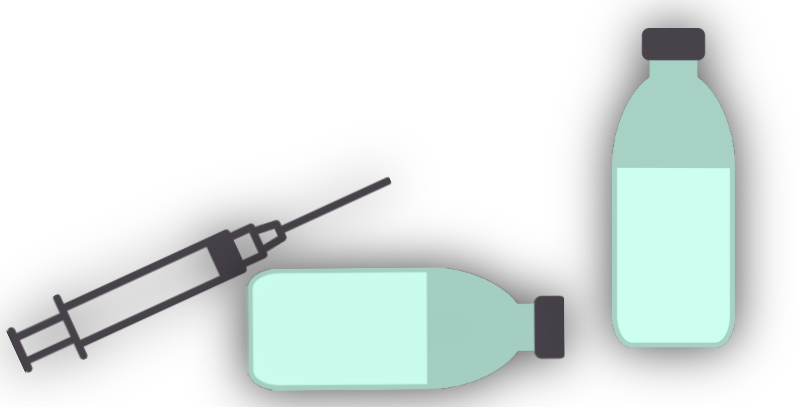
Naltrexone for Extended Release Injectable Suspension



Naltrexone ER: efficacy

Efficacious compared to placebo

- Comer: 60 U.S. heroin users, 8 weeks (retention in tx and opioid negative urines)
- Krupitsky: 250 Russian heroin users, 24 wks (retention in tx without relapse)

- Efficacious compared to buprenorphine
  - Tanum: Non-inferior to buprenorphine for decreasing opioid use at 12 wks
  - Lee: Non-inferior to buprenorphine for decreasing opioid use at 24 weeks

Comer Arch Gen Psych 2006
Krupitsky Lancet 2011
Tanum JAMA Psychiatry 2017
Lee Lancet 2017

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Outcome	XR-NXT (n=283)	BUP-NX (n-287)	Treatment Effect
Inducted to study medication (ITT)	204 (72%)	270 (94%)	OR 0.16, 0.09-0.28; P<0.0001
Relapse-free survival (weeks)	8.4 (3-23.4)	14.4 (5.1-23.4)	HR 1.36, 1.10-1.68; p=0.0040
	20.4 (5.4-23.4)	15.2 (5.7-23.4)	HR 0.92, 0.71-1.18, p=0.49
Opioid relapse, weeks 3-24	185 (65%)	163 (57%)	OR 1.44, 1.02-2.01; p=0.036
	106/204 (52%)	150/270 (56%)	OR 0.87, 0.60-1.25; p=0.44

Lee JD, et al. *Lancet* 2017

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Efficacy: conclusions

- All three medications are efficacious **once a patient is on the medication**
- Buprenorphine is equivalent to methadone in terms of decreased illicit drug at clinically useful doses
- Extended release naltrexone is equivalent to buprenorphine in terms of decreased illicit drug use.
- Both buprenorphine and methadone decrease mortality significantly

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Induction and other clinical variables

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Methadone induction

No need for withdrawal

Must occur at an OTP or in a hospital setting

BUT the risk of death while on methadone is highest during the initial four weeks of treatment, the induction phase

Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

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Buprenorphine induction

Requires a brief period of withdrawal (usually 8 – 18 hours off opioids) unless using microinduction

No increased mortality during induction

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Extended release buprenorphine: induction

XR buprenorphine: recommend 7 days SL first (8-24 mg)

Subcutaneous abdominal injection that HURTs

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Extended release naltrexone: induction

Requires abstinence from opioids 4 – 7 days

About 25% of patients will not complete induction

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Outcome	XR-NXT (n=283)	BUP-NX (n-287)	Treatment Effect
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Lee JD, et al. *Lancet* 2017

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Recent mortality data

- Original study found 2x the number of overdoses in the naltrexone arm, but not statistically significant

- Reanalysis of data: the original study had missed overdoses.
  - When those overdoses were counted, the hazard ratio for XR-naltrexone relative to bup/nal was 2.4 for overdose (19 in naltrexone arm, 9 in buprenorphine arm).
  - Statistically significant.
  - 1/3 of naltrexone overdose events occurred among participants who were not induced

Ajazi et al. JAM 2021

Other clinical/patient level considerations

- Prolonged QT, family hx of arrhythmia or sudden death – methadone risk
- Methadone is only dispensed at OTPs and patients must present daily for at least the first 90 days
- Known need for opioids in the future (surgery, sickle cell) – Naltrexone contraindication
- Safe place to store medication - methadone, buprenorphine consideration
- Other use disorders

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	Methadone	Buprenorphine	Naltrexone ER	Buprenorphine ER
Patient has difficulty with prescriptions	+	+/-	+	+
Daily dispense is problematic (illness, geography)	X	+	+	+
Patient does not have a place to store medication	+/-	+/-	+	+
Patient will require opioids in the future	+	+	X	+
A period of abstinence unlikely/difficult	+	+	X	+/-
Patient want this medication	+	+	+	+
Other clinical variables	+	+	+	+

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What questions, comments do you have?

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