UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

XR-NALTREXONE *for the* Treatment *of* OPIOID USE DISORDER:

WHEN & HOW TO GET STARTED

Matt Iles-Shih, MD

Acting Assistant Professor

UW Medicine & Harborview Medical Center

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

SPEAKER DISCLOSURES

✓ No conflicts of interest/disclosures

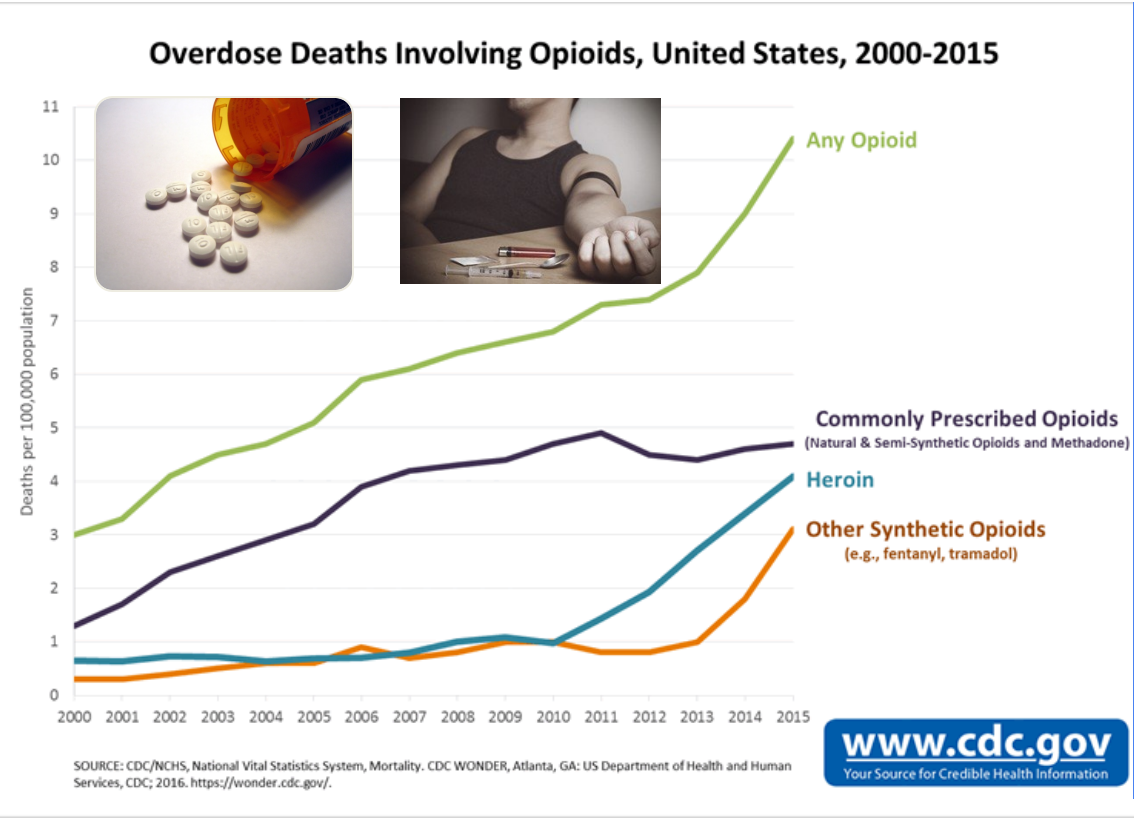
UW PACC

OBJECTIVES

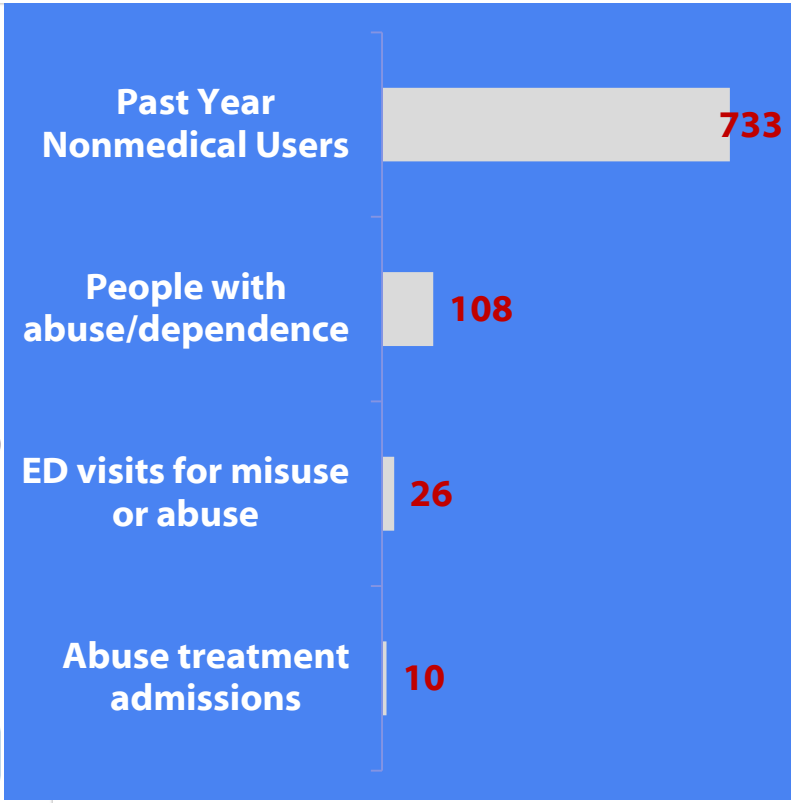
1. The role of Extended-release Naltrexone (XR-NXT) in treating OUD
   - The antagonist among agonists (MAT options)
   - When to use Extended-release Naltrexone (XR-NXT)
2. How do I start my heroin-using patient on Extended-Release Naltrexone?

UW PACC

QUICK REMINDER: WE'VE GOT A PROBLEM



For every 1 death in 2010, there were:



https://dawninfo.samhsa.gov/default.asp.

UW PACC

TWO CASES:

1. **Jenny:**
   - High functioning 47yo nurse now 4mo s/p abdominal surgery; was rx-ed oxycodone post-surgery, which she continued for 1.5 months. “My PCP said, ‘OK, that’s enough, we need to be careful with this [medication]’ and did a short taper” which pt found difficult to tolerate.
   - She found herself intermittently accessing older rxs in the family’s medicine cabinet. Concerned, she has stop misuse for the past month but says, “it’s weird, the thought is still there sometimes—not really strong right now but, you know, I work in a clinic setting…I guess sometimes I doubt myself, you known; I want to feel safe and confident in again.”

TWO CASES:

2. Rob:

- 32yo male w/extensive SUDs hx, including OUD, AUD, and hx of benzodiazapine misuse.
- Has been trialed on buprenorphine-naloxone & methadone at different times over the past 7yrs but has struggled with compliance and has been discharged twice from specialty clinics. He reports 2 accidental ODs.
- Continues to use heroin and, occassionally, illicit methadone as well as EtOH. States, “I don’t use xanax too much now…maybe sometimes.”
- Is interested in working towards sobriety, stating “I’m getting too old for this,” but struggles to commit to intensive treatment and states, “Look, I need to deal with one thing at a time here…I got to stop the heroin., the other stuff, maybe down the road.”

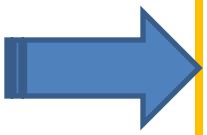
MATCHING PATIENT/CLIENT TO THE APPROPRIATE THERAPY

UW PACC

OUD TREATMENT: Where To Begin?

Screening & Assessment:

- SUDs & Psych:
  - SU hx (substances, timecourse, severity, sequelae, prior tx/rx exp., check PDMP!)
    - Opioids: which, duration, frequ, recency, risk of relapse
    - Active sed/hypnotic, EtOH use DOs?
  - Other psych comorbidities, hx of self-harm & current risk
- Gen. Med:
  - Active conditions, med hx, rxs
  - Evidence of intox/withdrawal
  - SU-assoc. conditions (abscesses, HIV, HepB/C, TB)
  - Cardio-pulmonary, hepatic, renal dysfunction
  - Labs: HCG, tox screen, BMP, LFTs, CBC, UA, ID screens (HepB/C, HIV, TB, syphilis)
- Psychosocial : safety, stability, rx-barriers, occupation, etc



Treatment

UW PACC

OUD TREATMENT: Where To Begin?

Indications & Conditions for Rx:

- Opioid use disorder
- Pt's preferences & engagement
- Clinical factors ID-ed in Evaluation

Potential treatment contexts:

- Inpt (managed detox)
- Residential Treatment
- Specialty outpt addictions
- Primary Care

Rxs (MAT):

- Buprenorphine
- Methadone
- XR-Naltrexone

Psychosocial Tx:

- MET, CMT, CBT, NA

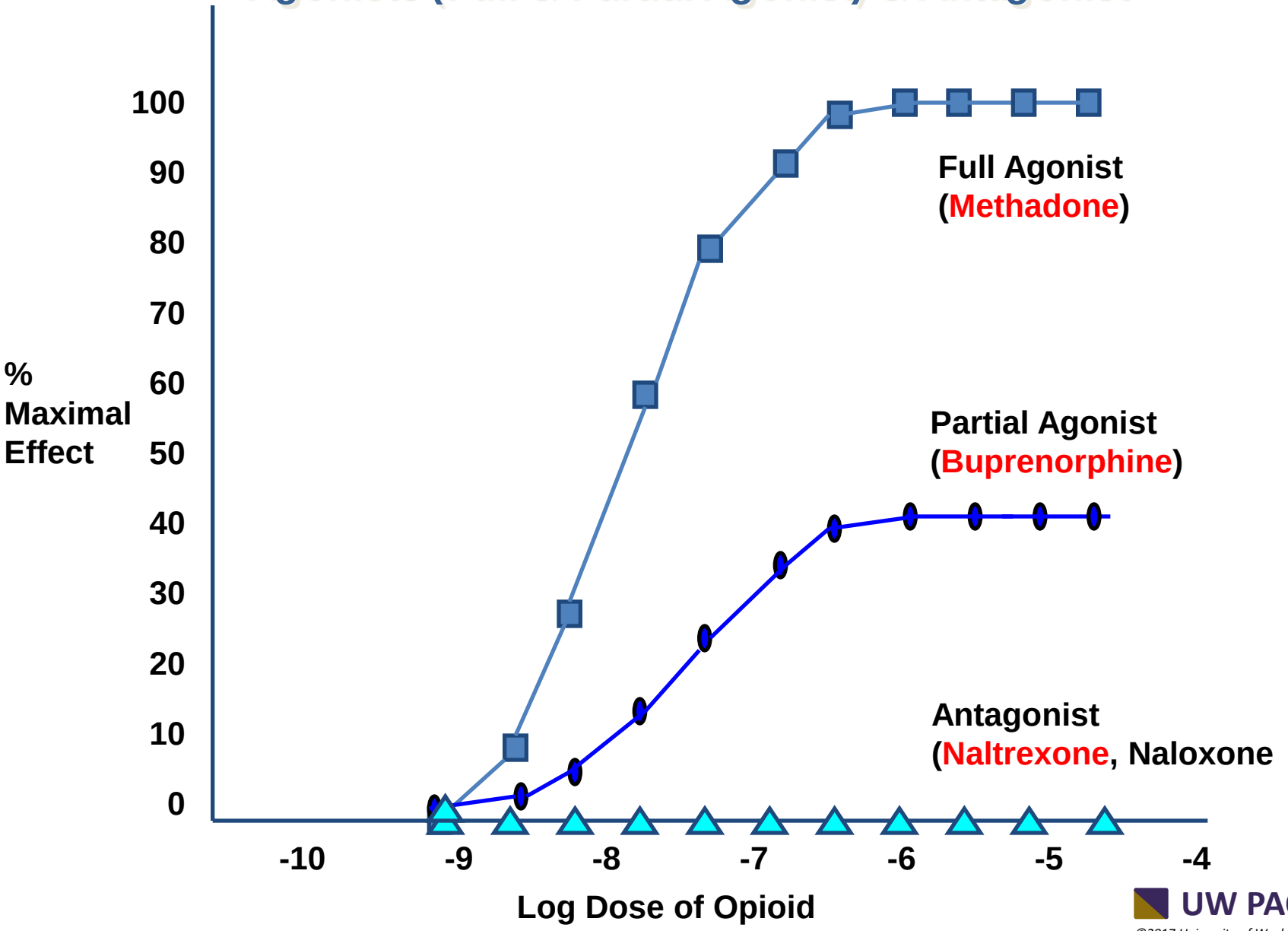
…& Rescue Kits:

- Naloxone kits (Prescribe them!)

UW PACC

Medication-assisted Treatment (MAT) Options:

Agonists (Full & Partial Agonist) & Antagonist



UW PACC

AGONIST THERAPY: 1ST LINE (FOR MOST PTS)

Studies have found:

- Reduced drug use
- Improved retention in treatment
- Improved health & functionality
- Public health gains (HIV, Hepatitis, etc.)
- Overall health care cost savings
- Reduced criminality (mixed results)
- Reduced mortality (mixed results)
- **Generally considered superior to Naltrexone (for most pops/clinical settings)**

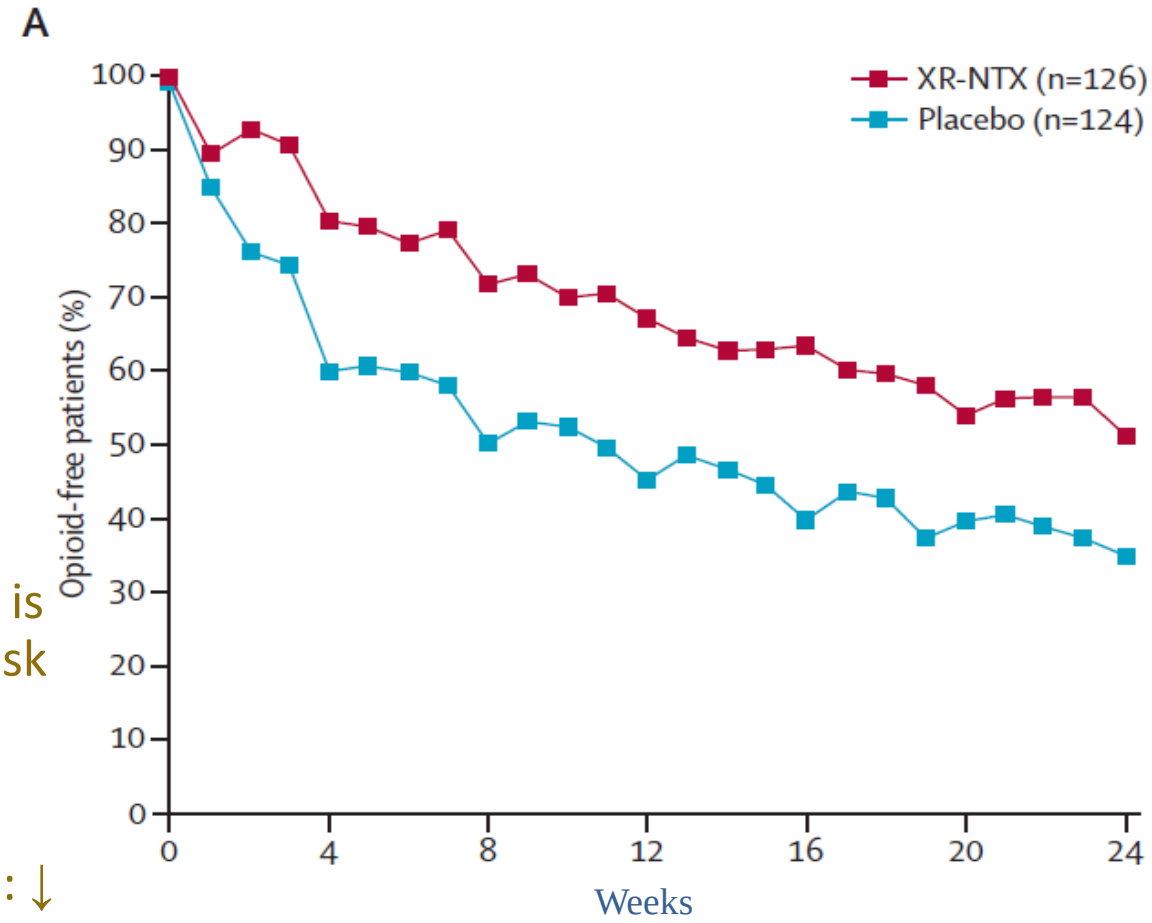
Gunne & Gronbladh, 1981; Mattick, RP et al, 2009; Mattick, RP et al., 2014; Kimber, J et al, 2015

UW PACC

XR-NTX (2ND LINE FOR MOST, 1ST LINE FOR SOME PTS)

- Effective if (a) initiated and (b) maintained

- Challenges:
  - Induction:
    - Agonist → XR-NTX is time of ↑ relapse risk
  - Retention in Treatment:
    - Receptor blockade: ↓ agonist effects; ↔ drive to use (at least directly)



Krupitsky, et al., 2011. Lancet 30, 377: 1506-13

UW PACC

MAT: Who's Appropriate for Which Rx?

Opioid agonists (full & partial)

- 1st line for most pts w/moderate-severe OUD
- If not using OAT, should have a good rationale

Who is appropriate for XR-NTX?

- Group #1: Are highly motivated and…
  - OUD of limited duration, mild severity &/or
  - Work related proscriptions against OST (e.g., CDLs, pilots, some HC workers), &/or
  - Clinical context w/enhanced supervision/structure
  - Strong personal preference to be abstinent of all opioids.

UW PACC

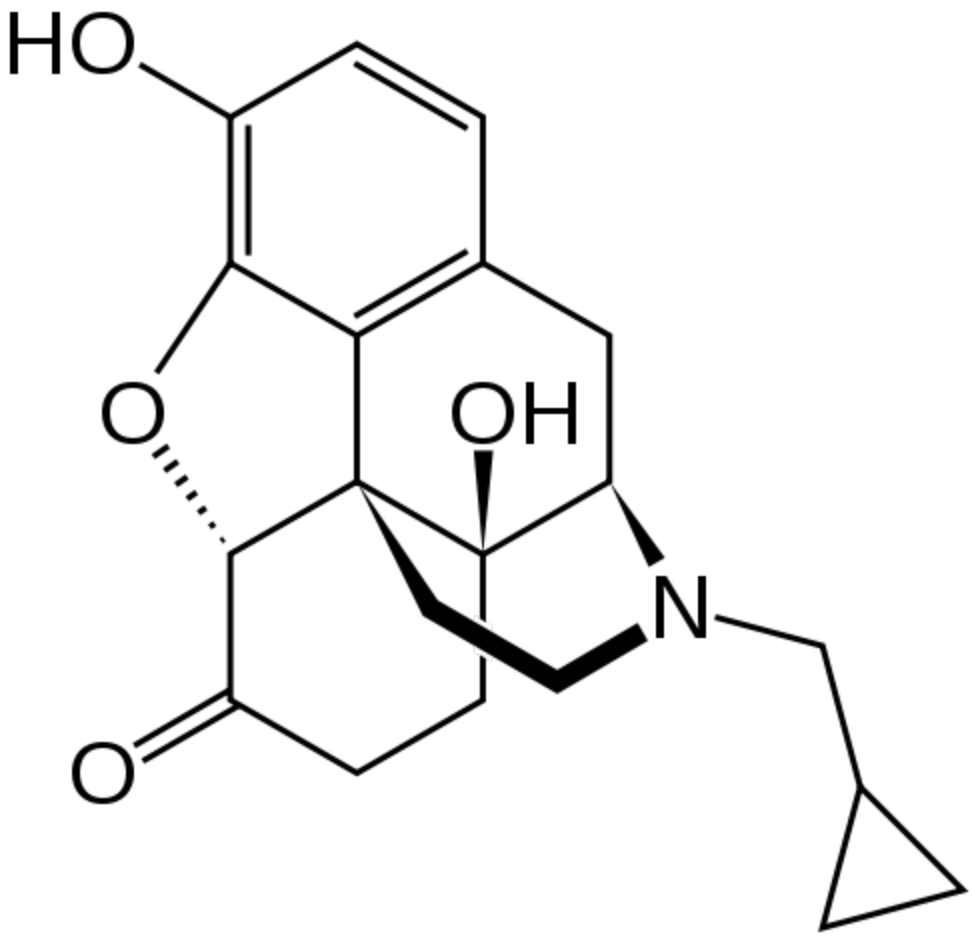
MAT: Who's Appropriate for Which Rx?

Who is appropriate for XR-NTX?

- Group #2: Pts with behaviors/circumstances that substantially impact safety, rx compliance
  - Concurrent EtOH/Sed-Hypnotic misuse despite treatment
  - Cont. illicit opioid-use despite adequate agonist MAT
  - Evidence of diversion
  - Significant, unstable psychiatric disorders
  - Medical comorbidities w/risk of opioid-assoc. symptom exacerbation (e.g., ongoing acute pain-management, severe pulmonary ds.)

- Group #3: agonist therapy is not available
  - Institutional barriers, lack of local prescribers, etc.

NALTREXONE



UW PACC

NALTREXONE

Use: opioid- (& alcohol)-use relapse prevention (for non-OAT candidates)

MOA: opioid receptor antagonist (high Mu affinity)

Dose & Route: 380mg IM (gluteal, superior-lateral quadrant) Q4wks

Pharmaco-dynamics/kinetics:

- Peak: biphasic w/ ~2hrs and then 2-3days
- Duration & Half-life: 4wks; 5-10 days.
- Metabolism: Primarily hepatic via non-cytochrome-mediated dehydrogenase (to 6-β-naltrexol); IM naltrexone ↓ 1st pass metab. Excreted in urine

UW PACC

NALTREXONE: SPECIAL POPS

- Infant: Excreted in breast milk (avoid if possible)
- Pregnancy: not well studied (some development abnl in animal studies)
- Geriatric: same as adult
- Hepatic & renal impairment:
  - no adjustment for mild impairment
  - caution w/severe impairment (poorly studied)

NALTREXONE: CAUTIONS & MONITORING

Potential SEs/Issues:

- Hepatocellular injury (rare, dose-dependent)
- Injection site rxs (vivitrol)—rarely clinically signif.
- Precipitated w/d (→ rx discontinuation)
- Analgesic blockade complicating pain management
  - Provide med alert bracelet
- Risk of OD: if pt stops (loss of tolerance) or attempts to overcome blockade

Monitoring:

- LFTs at initiation, at 1 mo, then annually

GETTING STARTED (FINALLY!)

XR-Naltrexone Induction

UW PACC

XR-NTX INDUCTION: HOW TO GET STARTED

1. The "traditional" approach:

- Med-managed withdrawal (for pts actively using):
  - ≤ 7days w/agonist or clonidine vs.
  - Stabilization & taper w/agonist
- Pt should be opioid-free for "7-10 days" prior to XR-NTX induction
- Withdrawal sx management w/ancillary meds
- Often w/:
  - Naloxone challenge prior to induction (most common), or
  - Trial PO naltrexone to ensure tolerability (less common)

UW PACC

“TRADITIONAL” XR-NTX INDUCTION PROTOCOLS

Day	"Standard" Withdrawal Management --> XR-NTX Protocols					
	Non-opioid Protocol			Buprenorphine Protocol		
	Agonist / Antagonist	Ancillary (scheduled)	Ancillary (PRN)	Agonist / Antagonist	Ancillary (scheduled)	Ancillary (PRN)
1	[7-day Washout]	Clonidine 0.1-0.2 Q2hr X 4 (NTE 1.2mg)	[1] Clonidine 0.1 Q6hr (NTE 1.2mg/d)	[Patient Abstinent]	--	--
2		Clonidine 0.1-2 QID	[2] Loperamide 4mgX1 then 2mg Q2h (NTE	Bup. 2mg SL Q1-2hrs PRN (Max daily dose = 8mg)	--	[+/- PRN meds withdrawal symptoms]
3			[3] Hydroxyzine 25-50mg Q6hr	Bup. 6mg SL	--	
4			[4] Dicyclomine 20mg Q8h	Bup. 4mg SL	--	
5		Clonidine 0.1-0.2mg TID	[5] Prochlorperaz. 10mg Q8h	Bup. 4mg SL	--	
6		Clonidine 0.1-0.2mg BID	[6] Methocarbamol 750mg Q8h	Bup. 2mg SL	--	
7		Clonidine 0.1-0.2mg Qday	[7] Ibuprofen 600mg Q6h	Bup. 1mg SL	--	
8	XR-NTX 380mg IM ‡	Clonidine 0.1-0.2mg Qday	*[8] +/- diazepam 5mg Q6h X 96hrs*	[7-day Washout]	--	
...	--	--	--		--	
15	--	--	--	XR-NTX 380mg IM ‡	--	--

‡ Challenge dose of Naloxone 0.8mg IM or Naltrexone 50mg PO often given prior to XR-NTX

UW PACC

XR-NTX INDUCTION: HOW TO GET STARTED

2. Newer Protocols for Faster Induction

- Sullivan et al (2017):
  - Randomized, open-label, controlled trial
  - 150 pts w/DSM-IV OUD (heroin, prescribed opioids)
  - Randomized 2:1 to NTX- vs. Buprenorphine-assisted outpt withdrawal protocol
  - Primary outcomes:
    - Successful XR-NTX induction
    - Receipt of 2nd XR-NTX inj (5wk s/p induction)

Sullivan et al (2017). Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. Am J Psychiatry 174:5, 459-67

SULLIVAN'S NTX- & BUP.-ASSISTED PROTOCOLS

	Treatment Protocol *					
	Naltrexone (Exp. Arm)			Buprenorphine (Control Arm)		
Day	Agonist / Antagonist	Ancillary (scheduled)	Ancillary, PRN (standing orders for all pts)	Agonist / Antagonist	Ancillary (scheduled)	Ancillary, PRN
1	[Patient Abstinent]	--	--	[Patient Abstinent]	--	--
2	Bup. 2mg Q1-2hrs PRN (Max daily dose = 8mg)	--	--	Bup. 2mg SL Q1-2hrs PRN (Max daily dose = 8mg)	--	[No standing orders; rxns given per clinical discretion]
3	[1-day Washout]	[1] Clonidine 0.1 mg QID [2] Clonazepam 0.5mg Q6h (as tolerated, max 2.0mg/d)	[1] Clonidine Q2hr 4 (max 1.2mg/d) [2] Prochlorperaz. 10mg TID [3] Trazod. 100mg, Zolpidem 10mg QHS	Bup. 6mg SL	--	
4	NTX 1mg PO †			Bup. 4mg SL	--	
5	NTX 3mg PO			Bup. 4mg SL	--	
6	NTX 12mg PO			Bup. 2mg SL	--	
7	NTX 25mg PO			Bup. 1mg SL	--	
8	XR-NTX 380mg IM			[7-day Washout]	--	
...	--	--			--	
15	--	--		XR-NTX 380mg IM ‡	--	

* Days #1-8, all patients were assessed daily for SU, vital signs, withdrawal symptoms, craving. After induction, all met weekly with a psychiatrist and attended twice weekly individual therapy focused on medication compliance (using elements of MET, CBT, relapse prevention.)

† One-time scheduled Prochlorperazine given with NTX on Day #4 only

‡ Challenge dose of Naloxone 0.8mg IM given prior to XR-NTX

Sullivan et al (2017)

NTX- vs. BUP.-ASSISTED OUTCOMES

Outcomes:

- Week #1 dropout and w/d severity comparable
- XR-NTX induction & 2nd dose (wk#5) ↑ for NTX arm
- Pts using heroin fairly worse across the board

		Treatment Arm (n=150)			Population
Outcomes		Naltrexone (n=98) %	Buprenorphine (n=52) %	Odds Ratio (XR-NTX vs. Bup.)	Odds Ratio (Rx opioids vs. Heroin)
1°	XR-NTX Induction	56.1%	32.7%	2.89 †	3.76 †
	2nd NTX Inj (5wks)	50.0%	26.9%	2.78 †	2.31 †
2°	Complete 8-day Detox	56.1%	46.2%		4.54 †
	Absintent wk 4-5 (s/p induction)	78.2% (43/55)	88.2% (15/17)		
	Mod-Severe Withdrawal	Treatment-Time Interaction: Bup = faster improvement in withdrawal scores vs. NTX †			

† Statistically significant at ≤ 0.05

UW PACC

OTHER STRATEGIES:

1. Inpatient/residential Settings: withdrawal management and induction in structured settings
   - expensive & not scalable
   - still w/high rates of AMA discharges & return to use

2. Minimize washout period for short-acting opioid users:
   - Look at misused substance's 1/2–life, conduct U-tox screens, & naloxone challenge.
   - Risk of precipitated withdrawal exp w/subsequent tx aversion

3. Stabilize on an agonist for ≥ 1 week, then gradually taper to XR-NTX
   - Not rigorously studied
   - May not be practical for many pts heading towards NTX

UW PACC

OTHER SUGGESTIONS
For facilitating MAT with XR-NTX

- Careful initial assessment; regular re-assessment
  - The shortest route to “there” depends on where “here” is
- Patient empowerment:
  - Longitudinal pt. education & collaborative treatment planning
- Strengthen Pt-clinician relationship:
  - Nurture trust & communication

- Well-managed withdrawal & induction
  - Tailored to the client/patient & to your clinic or practice
- Proactive maintenance rx (don’t let pt fall through the cracks)
  - Reach out to drifting pts
  - Pt tracking & reminders
  - scheduling appnts to coincide w/monthly injections
- Don’t give up!
  - Induction is a first step, sometimes repeatedly taken
  - Relapse prevention-planning

UW PACC

DISCUSSION:

- What's been your experience w/XR-NTX?

- What challenges & benefits have you run across (or might anticipate) for your clinic and patients?

UW PACC