MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

A Primer on Antagonist-Based Treatment of Opioid Use Disorder in the Office Setting

Adam Bisaga, MD
Professor of Psychiatry
Columbia University Medical Center, New York, NY

Adam Bisaga, MD, Disclosures

- Received free medication from Alkermes to support NIDA research
- Site PI on a multi-site clinical trial sponsored by Alkermes

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose thisinformation.

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Describe the evolution of antagonist-based treatment for opioid dependence
  - State the guidelines to select the most appropriate patients for treatment with naltrexone
  - Determine pharmacological strategies to initiate treatment with naltrexone
  - Identify clinical challenges encountered during treatment with naltrexone
  - Implement naltrexone in addiction practice competently

Workshop Outline

Naltrexone-assisted treatment of OUD

Section 1: Introduction to antagonist-based treatment of OUD	**Section 2**: Patient selection and treatment Initiation	**Section 3:** Maintenance treatment and treatment logistics	**Section 4:** Special Populations
Treatment of OUD using medications	Selection of patients: individualized treatment	Long-term treatment and treatment termination	Adolescents, dual diagnosis, medically ill, pregnancy
Neurobiology of OUD and MAT	Treatment initiation scenarios	Common clinical challenges	Naltrexone in criminal justice setting
Agonist vs. antagonist: advantages and limitations	Detoxification and NTX induction protocols	Safety concerns	Behavioral strategies to augment effectiveness of NTX
The evidence to support use of naltrexone	Managing patients during early stages of treatment	Logistics of using injectable naltrexone	Discussing NTX and recovery With patients and families
		Demonstration of medication preparation and administration	Integrating MAT with 12-step principles and fellowship

The goal of this training is to provide background information, practical resources, and guidelines to help clinicians adopt naltrexone in their treatment of patients with OUD

Section 1:

Introduction to antagonist-based treatment of OUD

Opioid Dependence Treatment Goals

- A range of treatment goals, individualized for each patient

minimization of harms from ongoing use ⟷ sustained recovery with abstinence from all substances and quality of life improvement

- Medically oriented treatment
  - Cessation of illicit opioid use
  - Protection against risk of OD and death
  - Improvement in physical and psychological health
- Behaviorally oriented treatment
  - Teach skills necessary to cope with cravings and life stressors without drugs
  - Helping patients become responsible for the management of their disorder
- The ultimate goal is to maintain long-term recovery with or without medication

Antagonist-based Treatment

- Opioid antagonist attach to the receptor and prevent other opioids from exerting any effects (receptor blockers)
- Naltrexone is a long-acting, high affinity, competitive opioid receptor antagonist with an active metabolite (6-β-naltrexol)
  - At sufficient plasma concentrations (>2 ng/ml) naltrexone fully blocks all opioid effects
- Naltrexone tablet is approved for the blockade of exogenously administered opioids
- Naltrexone injection (extended release) is approved for prevention of relapse to an opioid dependence following opioid detoxification
- Appealing choice for patients seeking detoxification from all opioids as a first stage of treatment

Treatment with Naltrexone: Components

- **Behavioral component**: blockade of the positive (reinforcing) effects of heroin leads to gradual extinction of craving and compulsive drug use
  - Patients who use heroin while taking naltrexone experience no euphoric effect and stop using
- **Pharmacological component**: naltrexone decreases reactivity to drug-conditioned cues thereby minimizing pathological responses contributing to relapse
  - Patients with a good clinical response to naltrexone usually have no urges to use
- As naltrexone has a different mechanism of action than agonists, it may address limitations related to treatment with agonists, providing another option for patients with opioid use disorder

Antagonist-based Treatment: limitations

- Requirement of detoxification and a wait-period of 7-10 days after the last dose of an opioid before antagonist can be initiated
  - A major barrier for many patients who find difficult to tolerate withdrawal
  - Further complicated by the reduction of inpatient/residential treatment programs
- Difficulty with the induction due to the possibility of precipitated or protracted withdrawal
  - Patients do not feel well at the beginning of the treatment
  - Requirement of close monitoring
- XR preparation of naltrexone is a relatively new medication with limited effectiveness research to date

Choosing Agonist vs. Antagonist Based Treatment

	AGONIST	ANTAGONIST
Maintains physiological dependence with withdrawal on stopping	+	-
Reinforcing effects promote medication adherence	+	-
Eliminates ongoing illicit opioid use	+	++
Protects against overdose during treatment	+	+
Increased risk of overdose after treatment dropout	+	+ (XR) ++ (oral)
Opioid side-effects (constipation, sexual dysfunction, sweating)	+	-
Euphoric effects if misused (potential for abuse and diversion)	+	-
Risk of overdose when combined with sedatives	+	-
Interferes with opioid-based pain management	+	++
Potential for tolerance development	+/-	-
Duration of treatment	?	?
Professional and public opposition and barriers to availability	+	+/-

Brief History of Naltrexone-based Treatment (1)

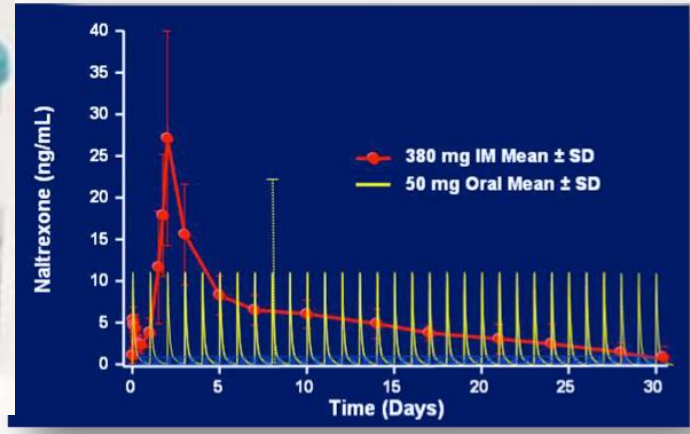
- First introduced in 1970s as oral preparations - with disappointing results
  - Difficulty with treatment initiation, low patient acceptability and poor compliance
  - Reviews concluded that there is no evidence that naltrexone is effective beyond selected patient groups which discouraged its clinical use
- 1980s brought new developments:
  - Clonidine found effective in treating withdrawal
  - Development of naltrexone-assisted detoxification methods
  - Buprenorphine was introduced for detoxification which facilitated naltrexone induction as compared to methadone-assisted method

Brief History of Naltrexone-based Treatment (2)

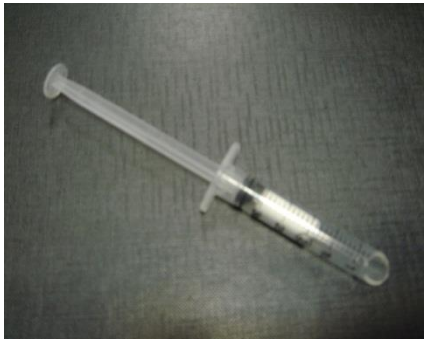
- Work with naltrexone continued in 1990s-2000s
  - Using antagonists during detoxification became an opportunity to continue with naltrexone as a relapse prevention agent: **Rapid Naltrexone Induction**
  - Behavioral therapy was developed to **improve adherence to oral naltrexone,** including elements of Motivational Interviewing, Cognitive Behavioral Relapse Prevention, Contingency Management, and involvement of significant others
  - **Long-acting preparations** of naltrexone become available to deal with non-adherence to oral preparations

Improving Treatment Retention Using Long-Acting Preparations

- Injections
  - 1st gen: oil suspension
  - 2nd gen: microspheres with NTX in suspension (Vivitrol licensed in 2007, approved by FDA for OUD in 2010)

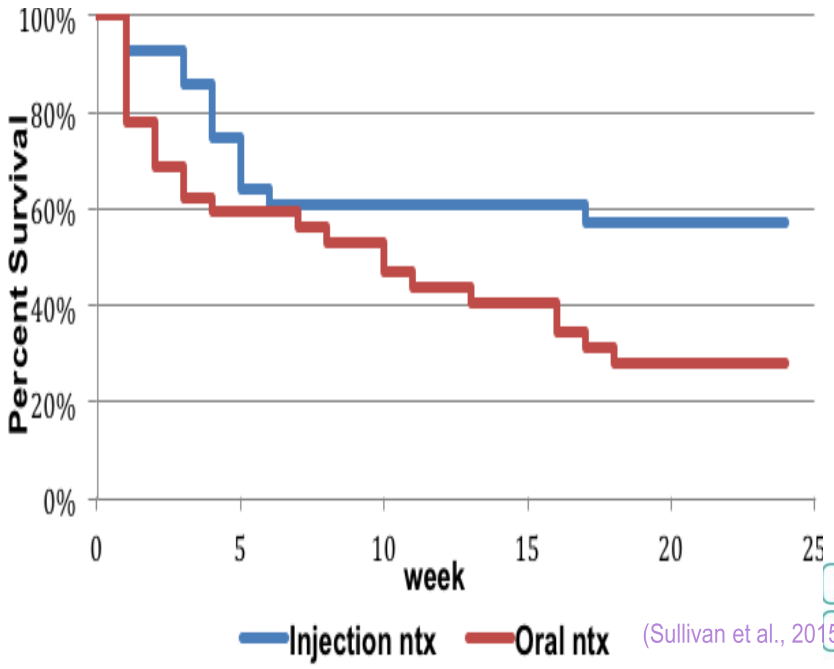


- Implants (not FDA approved)
  - 1st gen: compressed NTX c. 1996, now licensed in Russia (Prodetoxone)
  - 2nd gen: NTX mixed with polymer matrix c.2001 (Go-Medical)



Efficacy of Naltrexone: oral vs. extended-release injection

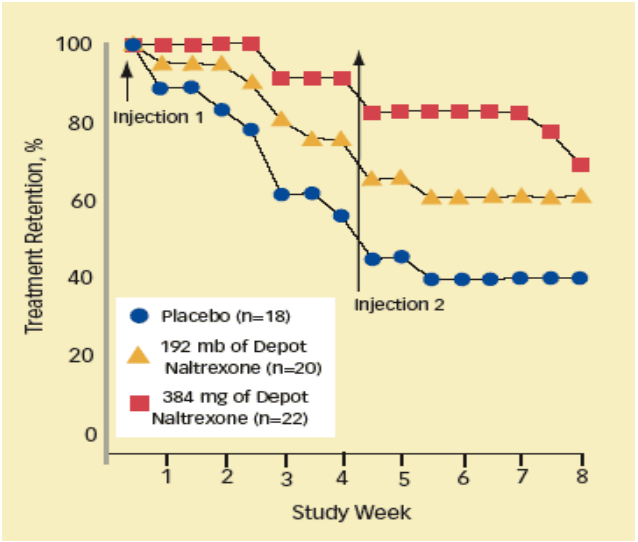
- Retention in treatment is often used as a primary outcome of treatment with naltrexone
  - Main reason for dropout is relapse and majority of patients retained in treatment are abstinent from opioids
- Treatment retention rate in groups treated with XR preparations is twice that of the oral group, approximating 50-70% at 6 months



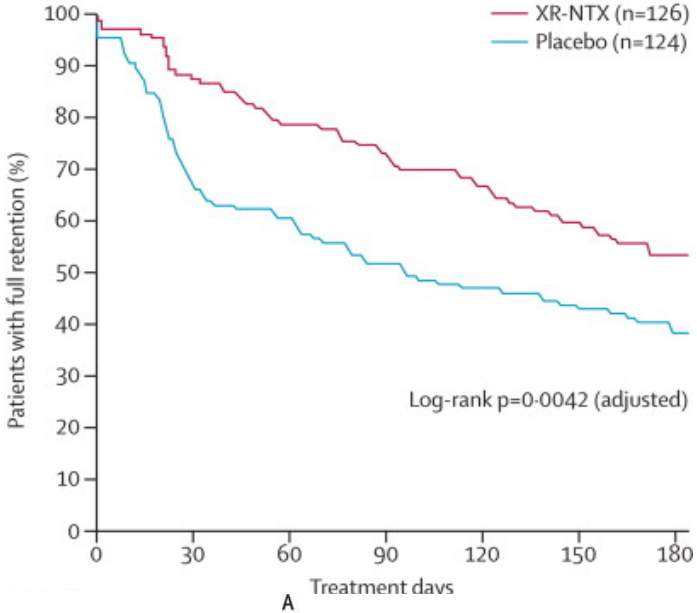
(Sullivan et al., 2015)

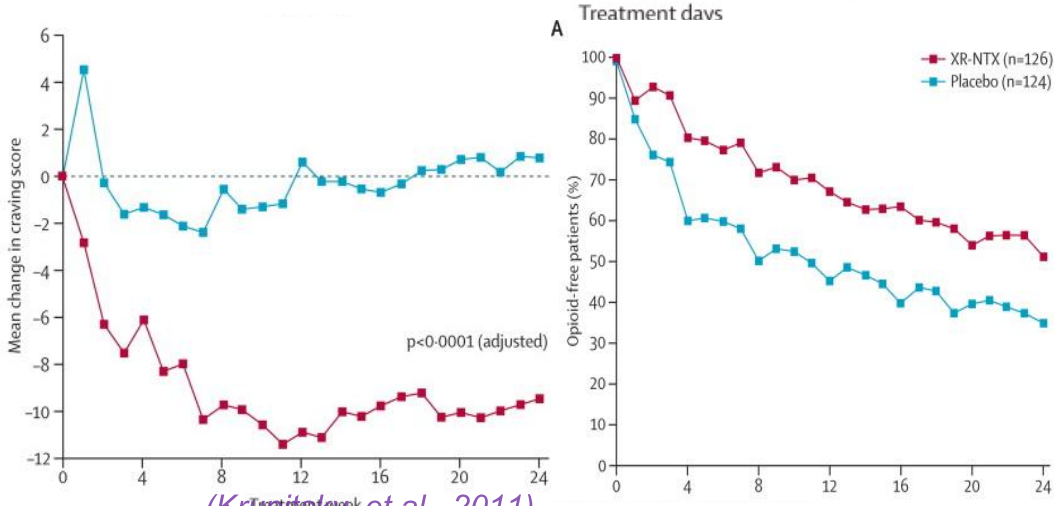
Efficacy of XR-Naltrexone vs. placebo

- Trials comparing injection of naltrexone vs. placebo showed that patients receiving active naltrexone have:
  - Better treatment retention
  - Less opioid use
  - Lower craving for opioids



(Comer et al., 2006)



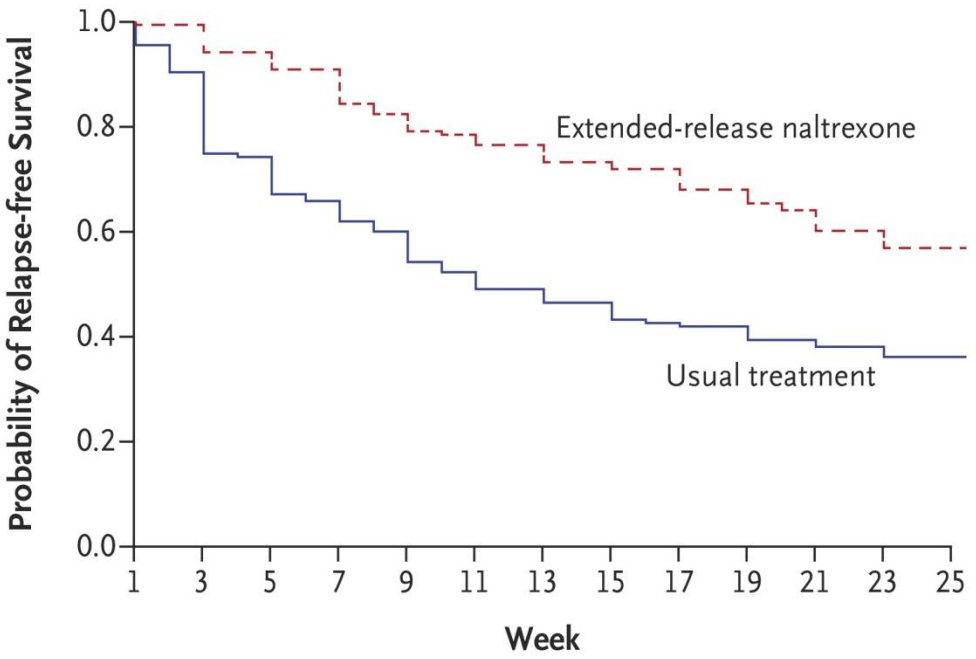


(Krupitsky, et al., 2011)

Effectiveness of XR-Naltrexone vs. Usual Treatment in Adults Involved in Criminal Justice System

- An open-label RCT compared XR-NTX to Usual Treatment among CJS-involved outpatients
- XR-NTX participants had
  - less relapse, longer relapse-free survival
  - less heroin use overall and fewer overdoses
- 61% of XR-NTX participants completed 24-weeks of treatment (6 injections)

Relapse-free Survival



No. at Risk													
Extended-release naltrexone	153	144	139	129	121	117	112	110	104	100	92	87	87
Usual treatment	155	116	104	96	84	76	72	67	65	61	59	56	56

(Lee, et al., 2016)

Efficacy of Naltrexone: Summary

- Extended-release preparation(s) of naltrexone are more effective than the oral preparation and should be the treatment of choice
  - Adherence to naltrexone is a challenge but it is better with XR preparation
  - Treatment should include emphasis on adherence
- Patients treated with XR-naltrexone have better treatment retention, lower opioid use and lower craving as compared to placebo
- Majority of patients retained in treatment with XR-naltrexone have low levels of concurrent opioid use
- XR preparation of naltrexone is a relatively new medication with small number of studies to date
- No direct evidence yet available comparing efficacy of XR-naltrexone vs. buprenorphine
  - Indirect comparisons show comparable treatment retention with lower level of ongoing opioid use

Section 2:

Patient selection and treatment initiation

Patients that might be Good Candidates for Naltrexone

- Patients who are not interested or able to be on agonist therapies
  - Highly motivated for abstinence from all opioids including methadone and buprenorphine
  - In professions where treatment with agonist therapy is still controversial (e.g., healthcare professionals, pilots)
- Patients who are abstinent from opioids but remain at risk for relapse
  - Released from a controlled setting (prison, residential program)
  - With increased stress or worsening of psychiatric problems
  - Moving back to neighborhood with greater exposure to drugs
- Patients who failed prior treatment with agonist
  - Continued cravings and use of illicit opioids, non-adherence with agonist medications, diverting/misusing agonists

Patients that might be Good Candidates for Naltrexone (2)

- Patients with less severe forms of a disorder
  - Short history of use, lower level of use
  - Individuals who use opioids sporadically
- Young adults living with involved parents who supervise treatment
- Young adults unwilling to commit to longer-term agonist therapy
- Individuals who use opioids sporadically and are at risk for progression to a daily use
- Patients successful on agonist therapy who wish to discontinue medication and may seek alternative treatment

Patients who may have good response to treatment with naltrexone

- Highly motivated patients who are committed to abstinence and engaged in recovery work
- Older patients with long history of use and multiple relapses
- Young adults living with involved parents who supervise treatment
- Patients with long periods of abstinence between relapses

Patient-Treatment Matching

- There is no evidence for patient-treatment matching from controlled trials, only from clinical experience
- Patients who were found to have good response to treatment with oral naltrexone
  - Highly motivated patients who are committed to abstinence and engaged in recovery work
  - Older patients with long history of use and multiple relapses
  - Patients with long periods of abstinence between relapses

When the Patient is Ready to Receive Therapeutic Dose of Naltrexone?

- Therapeutic doses of oral or injection naltrexone will precipitate severe an prolonged withdrawal in patients who are physically dependent on opioids or have large amount of opioids in their system
- Always confirm absence of opioids and physical dependence prior to the first dose of naltrexone
  - Urine drug screen must be negative for all opioids (morphine, oxycontin, buprenorphine, methadone, fentanyl) BUT some opioids may not be detected on the in-office urine toxicology screen (e.g., kratom)
  - Always perform naloxone challenge if unsure of the abstinence and the absence of physiological dependence
  - Patient must understand the risks of precipitated withdrawal if underreporting

Naltrexone and Opioid Withdrawal

- Naltrexone is an opioid receptor antagonist and can only be started in individuals who have completed opioid withdrawal
- When naltrexone is given to patients who are physically dependent (and have heroin in their system) naltrexone will displace heroin off the receptor and precipitate withdrawal symptoms within 30-60 minutes
  - As opposed to a slow onset of a spontaneous withdrawal
  - Precipitated withdrawal may present with atypical signs (e.g. delirium)

Naltrexone and Opioid Withdrawal: 2

- Even when urine toxicology turns negative (e.g., 48-72 hrs after the last heroin dose) patients are still physically dependent and naltrexone, especially in higher doses, will precipitate withdrawal
- The severity of precipitated withdrawal will be lower as the time since the last heroin dose gets longer and the dose of naltrexone is lower
- After 5-7 days since the last heroin dose, naltrexone should not precipitate any additional withdrawal
- BUT: the chance of relapse increases with every day that the patient is not receiving full dose of naltrexone

Main Withdrawal Approaches

- Agonist-assisted opioid withdrawal
- Symptomatic-only care
- Rapid withdrawal using antagonist
- Ultra-Rapid withdrawal under anesthesia

Agonist-assisted withdrawal

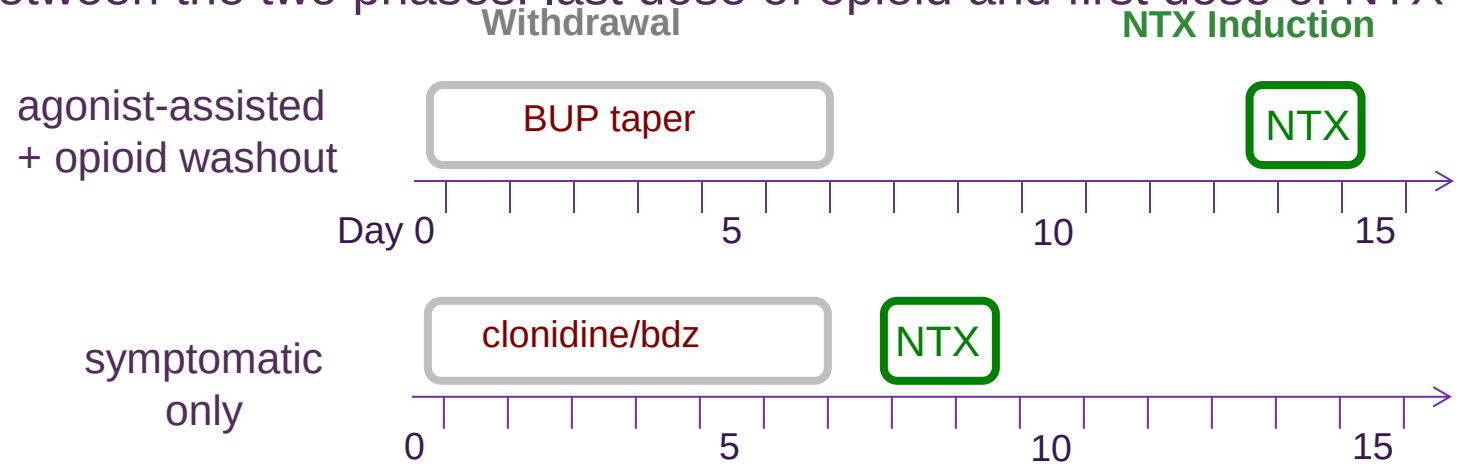
- Low doses of opioid agonist (methadone 10-20 mg or buprenorphine 4-8 mg) are given for 2-4 days to suppress severe opioid (heroin) withdrawal from emerging
- Subsequently agonist is tapered off slowly to minimize the severity of emerging withdrawal
  - Adjunctive medications (e.g., clonidine) can be used if agonist is tapered rapidly and after the last dose
  - Duration of agonist taper may be adjusted to minimize withdrawal severity in patients with high level of dependence
- Agonist-assisted withdrawal may minimize complications in medically or psychiatrically ill patients, and in those with physical dependence on alcohol or sedative-hypnotics
  - If needed, slow agonist taper allows for safe completion of withdrawal over an extended period of time (weeks)

Other Withdrawal Approaches

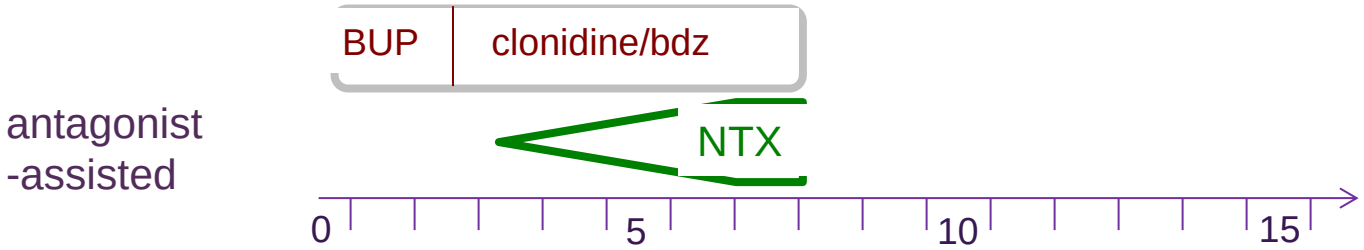
- Symptomatic-only treatment
  - A variety of adjunctive medications is used to decrease specific symptoms of withdrawal
- Rapid withdrawal using antagonist
  - Naltrexone is added 2-3 days after the last dose of opioid starting with very low doses (3-6 mg)
  - Emerging withdrawal symptoms are treated with adjunctive medications to minimize discomfort
- Ultra-rapid withdrawal under anesthesia
  - Withdrawal is precipitated with large doses of antagonist while the patient under a deep sedation or a general anesthesia
  - Not recommended by most guidelines (higher complications, including death, and minimal advantages)
  - May be appropriate in very selected, low risk cases after careful evaluation of risks and benefits

Initiating Naltrexone

- Two phases of treatment: 1) withdrawal, 2) naltrexone induction
- Current FDA-sanctioned method involves 7-10 days “washout” period between the two phases: last dose of opioid and first dose of NTX



- Not using agonist during withdrawal, shortens duration of “washout”



- Introducing naltrexone during withdrawal accelerates the process of induction

Naltrexone Induction Algorithms (Sigmon et al., 2012)

	Severity (physical dependence/anticipated withdrawal)	
	NONE Already abstinent (completed buprenorphine taper and has abstained for 7-10 days, exiting controlled environment)	**MILD** H: 1-2 bags/day; OXY: <50mg/day
Setting	**Outpatient**	**Outpatient or partial hospital**
Buprenorphine Dose	None	None or 4mg, day 1
Clonidine	None	0.1-0.2 mg TID to QID
Clonazepam	None	0.5 mg BID
Ancillary medications	None	Sleep, pain (e.g. NSAID)
Hydration	Routine	Aggressive oral hydration
Time to first NTX dose	Day 1	Day 3
Initial oral NTX dose	25-50 mg	12.5 mg QD
Time to XR-NTX injection	Days 1-2	Day 4; (or Day 5-6 after titrating oral naltrexone to 25-50mg QD)

Rapid Naltrexone Induction Algorithm *(continued)*

	Severity (physical dependence/anticipated withdrawal)	
	MODERATE H: 3-6 bags/day; OXY (50-100mg/day); following short-term methadone or buprenorphine taper	**SEVERE** > 6 bags/day; illicit methadone; severe prescription opioid use (>100 mg/day); significant medical problems
Setting	**Partial hospital with with inpatient backup**	**Inpatient or partial hospital with inpatient backup**
Buprenorphine Dose	4-8 mg, day 1 or 2	8 mg, day 1 or 2, or >8 mg as needed
Clonidine	0.2 mg (TID to QID)	0.2-0.3 mg QID
Clonazepam	1.0-2.0 mg (TID to QID)	1.0-2.0 mg QID
Ancillary medications	Sleep, pain, GI distress	Sleep, pain, GI distress
Hydration	Aggressive oral hydration	Aggressive oral or IV hydration
Time to first NTX dose	Days 3-4	Day 4-5 (later if needed)
Initial oral NTX dose	6 mg BID	3-6 mg QD-BID
Time to XR-NTXinjection	Days 4-5; or days 5-7 after titrating oral naltrexone to 25-50 mg QD)	Day 5-6; (or Day 6-7 after titrating oral naltrexone to 25-50mg QD)

Naltrexone Initiation During Withdrawal: Rapid Naltrexone Induction Procedure

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine	admission	4 mg bid					
Naltrexone				3 mg	6 mg	25 mg	50 mg po 380 mg im
Supportive medications	clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg tid, prochloperazine, zolpidem, trazodone						

- Protocol may be modified depending on the level of physiological dependence
- Low starting doses of naltrexone (1-3 mg) will minimize precipitated withdrawal while accelerating time to the full dose
  - At present, low-dose naltrexone is only available from compounding pharmacies
- Approximately 70% of patients complete inpatient and 60 % complete outpatient procedure and accept naltrexone injection

Buprenorphine Bridge (after Heroin) prior to Rapid Naltrexone Induction

	Day 1-10	Day 11-15	Day 16-20	Day 21-25	Day 26-30	Day 31	Day 32	Day 32	Day 33	Day 34	Day 35
Buprenorphine	8 mg	6 mg	4 mg	3 mg	2 mg						
Naltrexone								1-3 mg	6-9 mg	12-25 mg	380 mg im
Supportive medications					clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg tid, zolpidem, trazodone						

- An outpatient procedure appropriate for patients with severe use disorder (e.g., injecting large doses of heroin) and those who are not able to tolerate more rapid transition onto naltrexone
- A period of treatment with buprenorphine allows patients to stabilize (stop) their drug use first prior to undergoing opioid withdrawal

Transition from Buprenorphine Maintenance to Naltrexone

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine	2 mg qd						
Naltrexone				1-3 mg	6-9 mg	12-25 mg	380 mg im
Supportive medications	clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg tid, Prochloperazine, zolpidem, trazodone						

- Many people who are unable to taper off buprenorphine may have a greater sensitivity to withdrawal symptoms or an anxiety disorder both of which can benefit from ancillary medications and support/therapy
- Some of patients who stop buprenorphine maintenance experience protracted withdrawal (anxiety, low energy, or amotivation) that may benefit from symptomatic treatment

How to minimize the risk of precipitated withdrawal

- Confirm absence of physical dependence
  - Urine drug screen negative for all opioids (opiates, oxycontin, buprenorphine, methadone, fentanyl, tramadol)
  - Discuss with the patient the risk of precipitated withdrawal if underreporting
- Consider naloxone challenge
- Administer a test dose of oral naltrexone (low-dose e.g., 12.5-25 mg)
- If oral naltrexone is tolerated, administer XR-NTX injection
  - Need to wait at least 60 min after oral challenge before injection
  - Oral dose given in combination with naltrexone injection will assure that sufficient opioid blockade will be present during the first day

Section 3:

Maintenance treatment and treatment logistics

Clinical Challenges: Testing the Blockade

- It is expected that approximately a third of patients will ‘test’ blockade, often within 1-2 days after receiving XR-naltrexone
  - As blood level may be low the first 24hrs, oral supplementation may be considered on the first day
- Most commonly patients will “test” 1-2 times with small amounts of opioid during the first week of treatment, after which they are “reassured” that blockade works and do not resume use
- Some patients will use large amounts, for 1-3 weeks, but very few will persist in the use if they receive full blocking doses of the medication
  - Very few patients try intentionally to “override the blockade”
- Continuous blockade prevents patients from relapsing to physical dependence and many of those patients prefer to remain on the medication

Clinical Challenges: Managing Relapse

- Some patients have increased craving and may use 3-4 weeks after the injection
  - in those more frequent injection (every 3 weeks) or oral supplementation may be considered
- Most commonly, the first sign of relapse is missing doses/injections. The blockade wears off 2-3 days after oral and 5-6 weeks after injectable doses
  - Additional therapy, involving network members, is useful to improve adherence
  - Inpatient stabilization and another attempt at antagonist treatment
  - Residential treatment/sober house
  - Transition onto agonist

Managing Severe Pain

- First try full doses of NSAIDs (e.g., ketorolac injection)
- For persistent or intolerable pain try regional nerve blocks
- High potency opiates (fentanyl or buprenorphine) can override blockade, anesthesiology involvement is necessary
- Patients should wear medical bracelet or wallet card with a 24-hr contact number

Safety Concerns: Overdose

- Risk of overdose is significant if patient decides to stop taking naltrexone, stop attending treatment, and resumes opiate use
- Provide a detailed description of risks (e.g., treatment agreement), continue discussing risks in patients who continue use:

  "I understand that after I stop naltrexone I may be more sensitive to the effects of heroin and any other narcotics. The amount of heroin or narcotics I may have been using on a routine basis before I started naltrexone, might now cause overdose and death. I ***fully understand the nature and seriousness of this possible consequence.***

  If I am not sure that I can avoid opiate use*, I understand that I can be referred to alternative treatment programs, such as a methadone maintenance, which is an effective treatment for heroin dependence and has a reduced risk of fatal overdose."*

- Risk of overdose applies to any completed detoxification or discontinuation of agonist maintenance. Naltrexone, especially long-acting may be protective against overdose for its duration of action.

Controversies Surrounding Antagonist Based Treatment: OVERDOSE

- Overall, treatment with agonist or antagonists reduces mortality as compared to drug-free treatment
- The risk of overdose is comparable while patients are **in active treatment** with MAT (adherent to naltrexone oral/XR, buprenorphine, or methadone)
- Mortality rates differ between patients who **discontinue treatment** with various medications
  - higher in patients treated with oral naltrexone as compared to methadone
  - higher in patients treated with oral vs. XR-naltrexone
  - comparable in patients treated with XR-naltrexone and methadone
- The long “tail” on the serum XR-naltrexone curve may provide protection during early drug-free period which is often marked by an elevated mortality

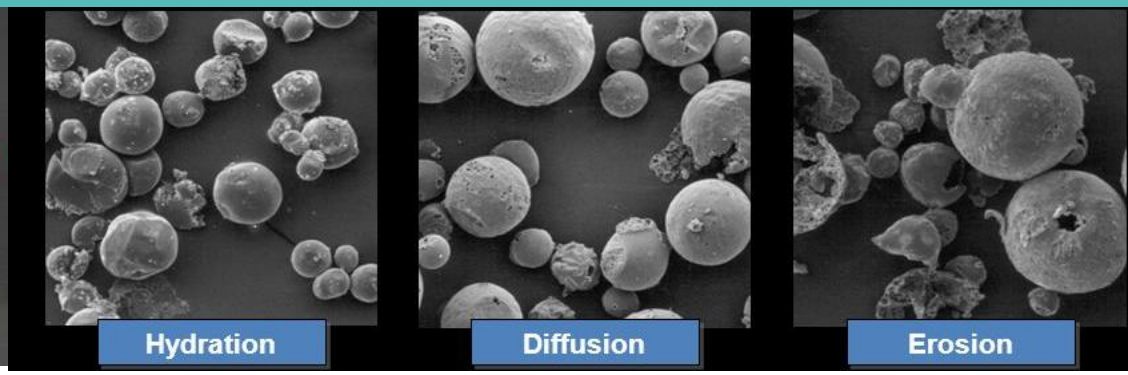
Controversies Surrounding Antagonist Based Treatment: DEPRESSION

- There are concerns about safety of this treatment: whether treatment with naltrexone increases risk of depression and suicidality
  - Though theoretically plausible, there is no systematic clinical evidence that naltrexone increases depression in this population
  - Some patients may indeed have depressive symptoms, usually during the first few weeks of treatment (naltrexone-induced vs. protracted withdrawal?)
  - Depressive symptoms usually improve during early abstinence from opioids
- Opioid Use Disorder is a risk factor for suicide: 10% vs. 1.3% in the general population
- Depression and suicidality warning is included in the package insert for Vivitrol
  - Suicidality was reported in 5% of patients treated with Vivitrol (10% in oral naltrexone) in open-label long-term US safety study
  - No such warning on buprenorphine package insert

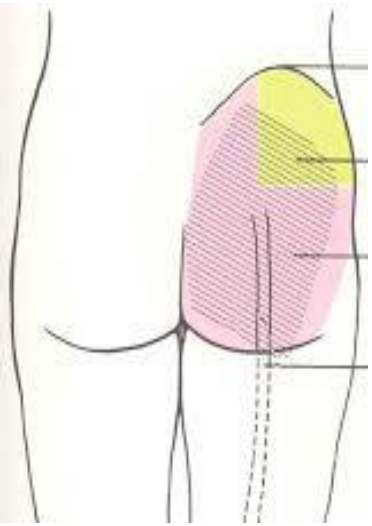
Treatment Termination

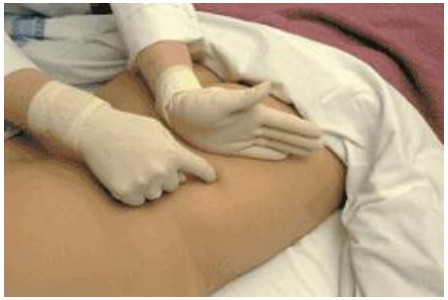
- For many patients opioid dependence is a chronic and relapsing condition
  - Demands long-term treatment with intensity matching the severity and response to treatment
- Duration of treatment with naltrexone positively correlates with favorable outcome (relapse prevention)
  - It is not known what (if any) duration of treatment will reduce the risk relative to that of a general population
  - Ongoing psychosocial treatment and linking with long-term recovery-support services is necessary to sustain benefits of MAT
- Recommended duration of treatment with naltrexone in patients who achieved full remission and abstinence
  - Minimum: 6 months
  - Optimal: 1 year, but longer duration prevents relapse risk in the long run

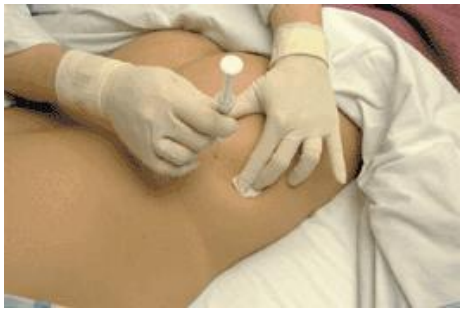
Injectable Naltrexone: Vivitrol

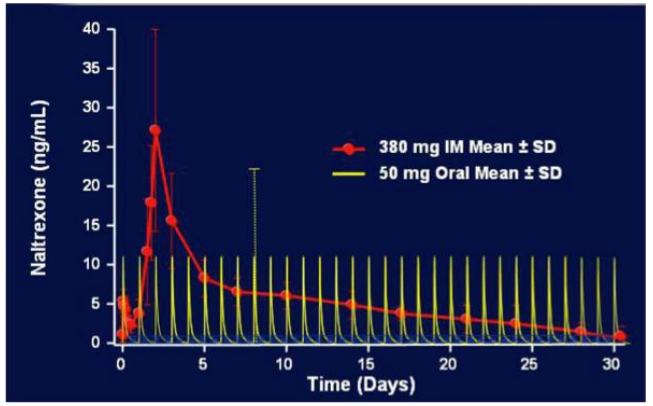


Microspheres technology
Polymer metabolized to CO_2 and H_2O









Total AUC is 4x that of oral naltrexone:
380 mg im =1500 mg p.o.

PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

References

- Brewer C, Wong VS. 2004. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. Addict Biol 9:81-7.
- Brooks A, Sullivan MA, Comer SD, Bisaga A, Carpenter KM, Raby, Yu E, O'Brien, and Nunes EV Long acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: A quasi-experiment. J Clin Psych, 2010:1371-8.
- Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, et al. 2006. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry 63:210-8.
- Greenstein RA, Arndt IC, McLellan AT, O'Brien CP, Evans B. 1984. Naltrexone: a clinical perspective. J Clin Psychiatry 45:25-8.
- Greenstein RA, Evans BD, McLellan AT, O'Brien CP. 1983. Predictors of favorable outcome following naltrexone treatment. Drug Alcohol Depend 12:173-80.

References

- Hulse GK, Morris N, Arnold-Reed D, Tait RJ. 2009. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry 66:1108-15.
- Judson BA, Goldstein A. 1984. Naltrexone treatment of heroin addiction: one-year follow-up. Drug Alcohol Depend 13:357-65.
- Kleber HD, Kosten TR. 1984. Naltrexone induction: psychologic and pharmacologic strategies. J Clin Psychiatry 45:29-38.
- Krupitsky, E., Zvartau, E., Blokhina, E., Verbitskaya, E., Wahlgren, V., Tsoy-Podosenin, M., Bushara, N., Burakov, A., Masalov, D., Romanova, T., Tyurina, A., Palatkin, V., Slavina, T., Pecoraro, A., Woody, G.E., 2012. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Arch Gen Psychiatry 69, 973-981.
- Kunoe, N., Lobmaier, P., Vederhus, J.K., Hjerkinn, B., Hegstad, S., Gossop, M., Kristensen, O., Waal, H., 2009. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. Br J Psychiatry 194, 541-546.

References

- Kunoe N, Lobmaier P, Vederhus JK, Hjerkinn B, Gossop M, et al. 2010. Challenges to antagonist blockade during sustained-release naltrexone treatment. Addiction 105:1633-9.
- Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA Jr, Wilson D, McDonald R, Rotrosen J, Gourevitch MN, Gordon M, Fishman M, Chen DT, Bonnie RJ, Cornish JW, Murphy SM, O'Brien CP. N Engl J Med. 2016 Mar 31;374(13):1232-42. doi: 10.1056/NEJMoa1505409. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders.
- Lobmaier PP, Kunoe N, Gossop M, Katevoll T, Waal H. 2010. Naltrexone implants compared to methadone: outcomes six months after prison release. Eur Addict Res 16:139-45.
- Ngo HT, Tait RJ, Hulse GK. 2008. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation. Arch Gen Psychiatry 65:457-65.
- O'Connor PG, Kosten TR. 1998. Rapid and ultrarapid opioid detoxification techniques. JAMA 279:229-34.
- Reece AS. 2009. Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. J Subst Abuse Treat 37:256-65.

References

- Sideroff SI, Charuvastra VC, Jarvik ME. 1978. Craving in heroin addicts maintained on the opiate antagonist naltrexone. Am J Drug Alcohol Abuse 5:415-23.
- Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice. Am. J. Drug & Alc. Abuse,2012, 38. 187-99.
- Sullivan, M.A., Rothenberg, J.L., Vosburg, S.K., Church, S.H., Feldman, S.J., Epstein, E.M., Kleber, H.D., Nunes, E.V., 2006. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial. Am J Addict 15, 150-59.
- Sullivan MA, Garawi F, Bisaga A, Comer SD, Carpenter K, et al. 2007. Management of relapse in naltrexone maintenance for heroin dependence. Drug Alcohol Depend 91:289-92
- Sullivan, M.A., Bisaga, A., Mariani, J.J., Glass, A., Levin, F.R., Comer, S.D., Nunes, E.V., 2013. Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade? Drug Alcohol Depend 133: 80-5.
- Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, Levin FR, Dakwar E, Mariani JJ, Nunes EV.Am J Psychiatry. 2017 Jan 10:appiajp201616050548. doi: 10.1176/appi.ajp.2016.16050548. [Epub ahead of print]. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine.

PCSS-MAT Mentoring Program

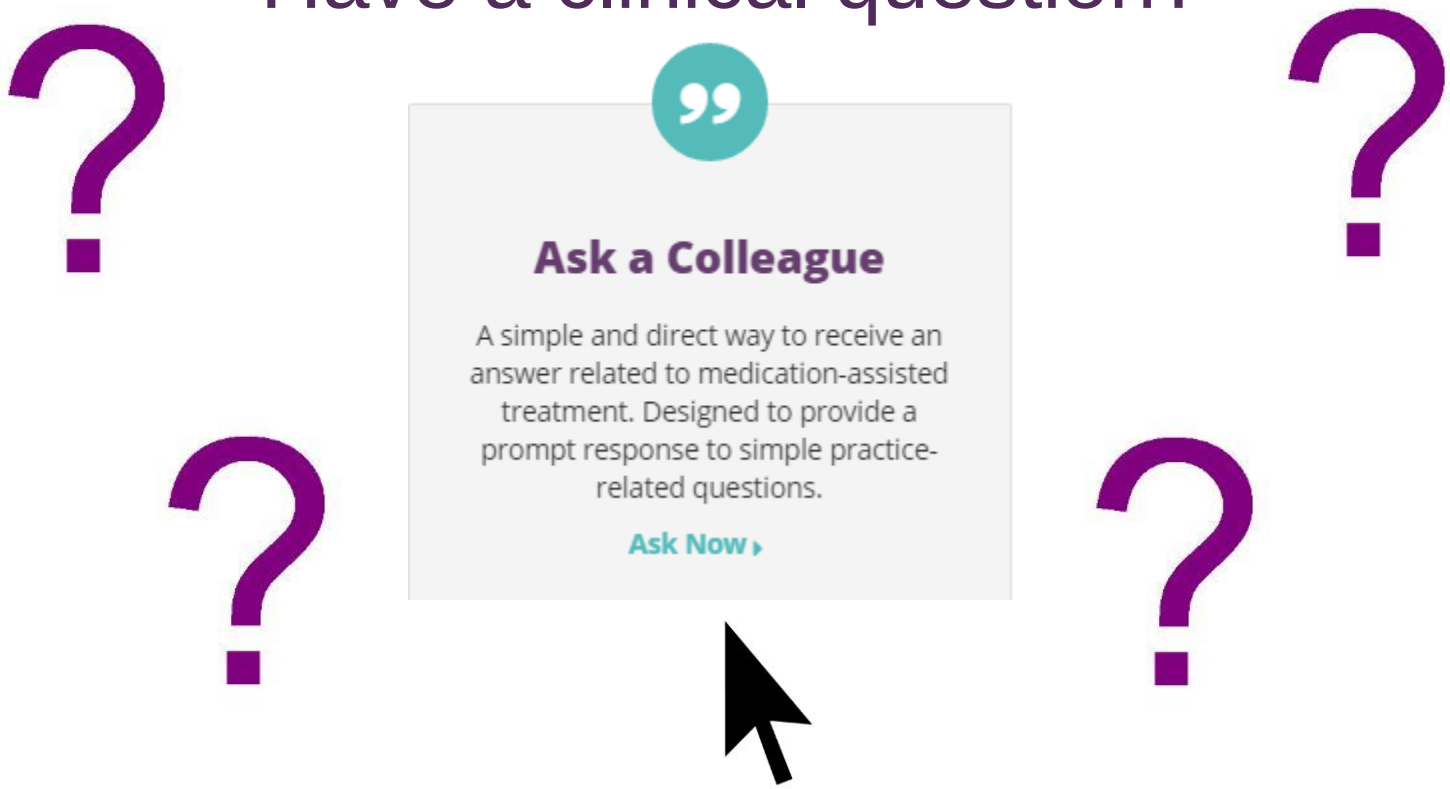
- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS-MAT Mentors are a national network of providers with expertise in **medication-assisted treatment and addictions**.
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

For more information visit:

pcssmat.org/mentoring

PCSS Discussion Forum

Have a clinical question?



PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

PCSS MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

PCSS-MAT is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with the: Addiction Technology Transfer Center (ATTC); American Academy of Family Physicians (AAFP); American Academy of Pain Medicine (AAPM); American Academy of Pediatrics (AAP); American College of Emergency Physicians (ACEP); American College of Physicians (ACP); American Dental Association (ADA); American Medical Association (AMA); American Osteopathic Academy of Addiction Medicine (AOAAM); American Psychiatric Association (APA); American Psychiatric Nurses Association (APNA); American Society of Addiction Medicine (ASAM); American Society for Pain Management Nursing (ASPMN); Association for Medical Education and Research in Substance Abuse (AMERSA); International Nurses Society on Addictions (IntNSA); National Association of Community Health Centers (NACHC); and the National Association of Drug Court Professionals (NADCP).

For more information: www.pcssmat.org

Twitter: @PCSSProjects

Funding for this initiative was made possible (in part) by grant no. 1U79TI026556-01 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

PCSS-MAT: Training, Mentoring, Resources