Clinical Advances in Non-agonist Therapies

Substance Abuse and Mental Health Services Administration
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NIH National Institute on Drug Abuse

Report of Proceedings

May 11, 2016

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2016 Clinical Advances in Non-agonist Therapies
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U.S. Department of Health and Human Services
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment

5600 Fishers Lane
Rockville, MD 20857

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FOREWORD

The nonmedical use of prescription opioid medications and heroin has become a major problem in the United States. The 2014 National Survey on Drug Use and Health found that 11.5 million persons aged 12 and above misused opioids, and 2.2 million persons aged 12 and above had an opioid use disorder (OUD) in the past year. Despite the magnitude of the problem, the research shows that nearly 80 percent of people with OUD do not receive treatment. They lack treatment because of the limited capacity of providers to treat those with opioid addiction, lack of financial resources, negative public attitudes about addiction, and numerous other barriers to care. The negative attitudes affect not only those diagnosed with opioid addiction but also the healthcare professionals who provide services to them.[1]

Federal agencies are working to expand access to treatment for OUD beyond specialized opioid treatment programs by encouraging medication-assisted treatment (MAT), which combines behavioral therapy and medications and can be provided in medical offices and other settings. Researchers, federal agencies, and pharmaceutical manufacturers have been focusing their attention on the development of medications that can be used to treat alcohol and OUDs.

Their efforts have resulted in the Food and Drug Administration (FDA) approving three products for treating OUD and preventing the occurrence of relapse: methadone, buprenorphine (alone and in combination with naloxone) and naltrexone (in oral formulation and as an extended-release injectable formulation, XR-NTX). These medications have been shown to be effective, safe, and cost-effective treatments when used and monitored properly.

In September 2014, the Substance Abuse and Mental Health Services Administration (SAMHSA)/Center for Substance Abuse Treatment (CSAT) and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) convened a 2-day Buprenorphine Summit. The meeting was called because even though the FDA had approved the use of buprenorphine for the treatment of OUD in 2002, many people who could benefit from it were not being offered buprenorphine as an option. At the Summit, federal and nonfederal leaders in the field of addiction treatment explored current data about the adoption of buprenorphine to treat OUD; the reasons for it not being widely prescribed; and strategies that federal agencies, medical professionals, and other concerned individuals might use to make the treatment more accessible to people with OUD.

In an effort to continue the exploration of treatment options for people with OUD, SAMHSA/CSAT, in partnership with NIDA, held a Clinical Advances in Non-Agonist Therapies Meeting at the SAMHSA headquarters on May 11, 2016. It was attended by approximately 40 people from federal agencies, medical professional organizations, universities, and private organizations, including a pharmaceutical company.

The goal of this meeting was to discuss federal, state, and local MAT initiatives/therapies, with an emphasis on XR-NTX (the injectable form of the drug, developed more recently than oral naltrexone), and to identify research on clinical therapies for MAT generally and for XR-NTX specifically. The main objectives of the meeting were: (1) to highlight where XR-NTX has been used successfully; and (2) to identify lessons learned that may be used to expand MAT implementation and access to XR-NTX and future non-agonist therapies.

[1] Source: Clinical Use of Extended Release XR-NTX in the Treatment of Opioid Disorder-A Brief Guide, Substance Abuse and Mental Health Services Administration, Rockville, Maryland, February 2, 2015, Page 1.

EXECUTIVE SUMMARY

Background:

The Clinical Advances in Non-agonist Therapies Meeting took place at the SAMHSA headquarters on May 11, 2016, sponsored by the SAMHSA/CSAT, in partnership with NIDA of NIH. It was attended by approximately 40 people from federal agencies, medical professional organizations, universities, and private organizations, including a pharmaceutical company.

The goal of this meeting was to discuss federal, state, and local MAT initiatives/therapies, with an emphasis on XR-NTX, a fixed 380 mg dose of the injectable form of naltrexone administered intramuscularly every 28 days, and to identify research on clinical therapies for MAT generally and for XR-NTX specifically. The main objectives of the meeting were: (1) to highlight where XR-NTX has been used successfully; and (2) to identify lessons learned that may be used to expand MAT implementation and access to XR-NTX and future non-agonist therapies.

Meeting Highlights:

OUD Non-agonist Medication Research: Current research shows that XR-NTX is effective at preventing relapse to opioid dependence in combination with psychosocial treatment in multiple populations. XR-NTX and emerging medications (e.g., lofexidine, a possible agent for medical withdrawal management prior to induction for MAT) are methods of allowing healthcare providers to tailor MAT to the genetic and psychosocial characteristics of the patient. Clinicians need support for the administration of XR-NTX medications as part of the treatment plan for patients. Patients should also be offered psychosocial treatments.

- **Future Directions**: Eliminating barriers to the access and use of non-agonist therapies, and increasing our understanding of optimal practices, such as identifying how best to integrate non-agonist and psychosocial therapies, better defining maintenance and patient retention, and determining the optimal duration of MAT treatment.

Clinical and Provider Considerations: Attention needs to be given to how best to administer XR-NTX and implement other MAT strategies, including assessment, initiation of treatment, and patient monitoring. Another area for consideration is the support clinicians require when starting to administer MAT, including XR-NTX, beyond the directions and guidance provided in medication inserts. Treatment systems should consider how to address patient/provider decision-making, as well as manage overdose risk in patients treated with XR-NTX, expand XR-NTX in criminal justice settings, integrate non-physicians into delivery of XR-NTX systems, and increase access to XR-NTX via pharmacies

- **Future Directions**: Providing clinical guidance in the areas of obtaining patient history—including a medical, psychiatric, and substance use history—as well as an evaluation of family and psychosocial supports; assessing and explaining risks/benefits of pharmacotherapy based on data (treatment options including medication options); documenting progress; and making shared decisions.

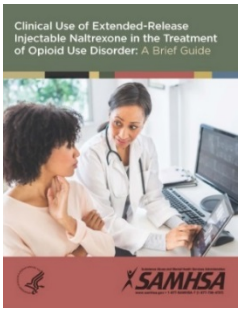
Special Populations: There is a need for patient education and choice regarding MAT using XR-NTX and other medications. XR-NTX and other MAT may benefit different populations including individuals in the criminal justice system (pre-/post-release), patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), American Indians and Alaska Natives, adolescents and young adults, and individuals with co-occurring disorders.

- **Future Directions**: Developing patient information on the spectrum of substance use disorders (SUDs) and treatment options, including MAT medications, developing patient-treatment matching protocols, and shared decision-making with clinicians.

In summary, understanding how to best utilize non-agonist medications as part of MAT requires exploring access in diverse medical settings, delivering patient-focused services and quality care, addressing the needs of special populations, implementing non-agonist MAT to increase diversion control, and building effective infrastructures. Addressing these key components is a critical step toward organizational engagement to reach all those in need of MAT for their opioid use disorder.

Meeting Outcomes/Products:

Additional SAMHSA Resources:
Additional relevant SAMHSA resources include the Medication-Assisted Treatment of Opioid Use Disorder Pocket Guide, the Medication for the Treatment of Alcohol Use Disorder: Pocket Guide, the Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide, and the Providers' Clinical Support System for Medication-Assisted Treatment (PCSS-MAT)



CLINICAL ADVANCES IN NON-AGONIST THERAPIES: PROCEEDINGS

Opening and Welcome

Opening Remarks

Dr. Kimberly Johnson, Director for the SAMHSA/CSAT, welcomed participants and thanked Dr. Mitra Ahadpour for organizing the meeting.

Welcome

Dr. Mitra Ahadpour, SAMHSA/CSAT Medical Officer, welcomed everyone and shared her appreciation for the work they are doing to address SUD. Dr. Ahadpour announced the purpose of the meeting and then asked the presenters to mention any conflict of interest they may have before making their presentations. She briefly reviewed the agenda and then introduced Dr. Joshua Lee, the meeting chair.

Participant Introductions

Dr. Joshua Lee welcomed all participants. Participants then introduced themselves and briefly shared their backgrounds in SUD treatment and in MAT, the use of medications to treat alcohol and/or opioid use disorder. (See Appendix A for a complete list of participants.)

Dr. Ahadpour then explained that the product from the meeting would be a summary report that would focus on the adoption of naltrexone for SUD treatment and the way it could be used in the field. She added that the report will be placed in the SAMHSA store, where the public will have access to it.

Presentations and Discussions

Presenters and participants represented a variety of perspectives—including those of research, health care, public health, criminal justice, and law enforcement—regarding promising initiatives for non-agonist therapies in SUD, treatment, and recovery. Following are summaries of the presentations by 15 experts in the field to help federal, state, and local MAT programs better understand the research associated with XR-NXT for MAT.

Naltrexone: Overview and Opportunities for Psychosocial Treatments

The first two presenters provided an overview of naltrexone and opportunities for psychosocial treatments.

Naltrexone Pharmacology: Overview and Research

Presenter: David Gastfriend, MD, DFASAM, Scientific Advisor for the Treatment Research Institute; Chief Architect, CONTINUUM: The ASAM Criteria Decision Engine

(Conflict of interest disclosure: Consultant: Alkermes, Indivior, Kaleo; advisory board or committee: Alkermes, Indivior, Kaleo; equity holdings: Alkermes.)

Key points: XR-NTX offers systemic exposure four times greater than oral naltrexone, with less than one-third the monthly dose. Though it is more expensive than some other medications, it may be less expensive than methadone delivered in an opioid treatment program when potential healthcare cost savings are considered in the equation. The clinical approach should be psychosocial, anticipating—with the patient, caregivers, and supportive others—possible changes in cravings and opioid use over time and preparing for reinjection with counseling and contingency management. Clinical monitoring of liver function with XR-NTX should follow standard approaches for assessment of SUDs.

- The pharmacology of XR-NTX is different from that of oral naltrexone. The systemic exposure of XR-NTX is four times greater than oral naltrexone, with less than one-third the monthly dose. XR-NTX is an opioid antagonist with the highest affinity for the mu-opioid receptor; it has little or no opioid agonist activity and few intrinsic actions besides its opioid-blocking mechanism.
- The initial study of the administration of the XR-NTX was done in Russia to assess the efficacy, safety, and patient-reported outcomes of an injectable, once-monthly, extended-release formulation of naltrexone for the treatment of patients with opioid dependence after detoxification. The study found XR-NTX effective in promoting abstinence from opioids, reducing craving, and preventing relapse after detox across a range of demographics and severity of characteristics.
- An open-label, 24-month study of XR-NTX in the United States was conducted with opioid-dependent healthcare professionals. The study aimed to evaluate the long-term safety and tolerability of XR-NTX and the effect of XR-NTX on retention, rate of opioid-negative urines, relapse prevention, employment status or licensure status, craving, and quality of life. Of the 38 patients in the study, only 4 had positive usage urines, 3 of whom had only one positive urine each. Cravings dropped about 50 percent, and mental component scores rose to normal levels.
- A quasi-experimental study of healthcare costs in opioid dependence compared four agents, using insurance claims to determine total healthcare costs. This study compared XR-NTX, oral naltrexone, buprenorphine, and methadone. The findings indicated that the use of XR-NTX, an initially a more expensive medication, saves money downstream when all healthcare cost savings are factored in and costs about 50 percent less than methadone.
- An analysis across multiple studies of XR-NTX continuation after XR-NTX patients had been prescribed pain medication for pain incidents showed that 92 percent of these patients continued to get their next XR-NTX shot.
- A double-blind random control study indicated that cravings first decrease after the injection, then increase very slightly before the next injection, particularly during the first 3 months of treatment. The study showed that the longer it has been since a previous injection, the greater the likelihood patients will use opioids; also, the longer since a previous injection, the more likely that patients will discontinue treatment. The observed time course of change in craving, opioid use, and discontinuation was not different, however, between XR-NTX and placebo recipients. The study concluded that this effect therefore is not pharmacological, and the clinical approach should be psychosocial, anticipating with the patient, caregivers, and

supportive others and preparing for reinjection with counseling and contingency management.

- The following is a list of XR-NTX warnings and precautions:
  - Hepatotoxicity
  - Injection site reactions
  - Eosinophilic pneumonia
  - Hypersensitivity reactions
  - Unintended precipitation of opioid withdrawal
  - Opioid overdose at the end of a dosing interval, after missing a dose and following an attempt to overcome opioid blockade
  - Depression and suicidality
  - Intramuscular injections and coagulopathies
  - Vivitrol® (injectable XR-NTX) blockade interacts with pain management
  - Opioid withdrawal should precede injection
  - Interference with laboratory tests
- Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. It is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered. The margin of separation between the apparently safe dose of oral naltrexone and the dose causing hepatic injury appears to be only fivefold or less. Two studies have found, however, that Vivitrol does not appear to be hepatotoxic at the recommended dose (Lucey et al., 2008; Mitchell et al., 2012).
- Clinical monitoring of liver function is suggested, but constant liver function test (LFT) is not recommended. There was agreement that practitioners should not delay treatment to test for liver disease first. If a patient is receiving XR-NTX and drinks alcohol, there is no disulfiram-like reaction or medical necessity for XR-NTX discontinuation.
- In 15 studies of 1,683 patients treated with XR-NTX over 5,719 patient months, the number of patient overdoses while on XR-NTX was 4, and the number of deaths was 1.

Examination and Application of Psychosocial Treatments in Conjunction with Naltrexone

Presenter: Louis E. Baxter, Sr., MD, DFASAM, DABAM; Consulting Medical Director, Behavioral Health of the Palm Beaches; President and CEO, Professional Assistant Program of New Jersey, Inc.
(Conflict of interest disclosure: None reported.)

Key points: MAT for addiction should be treated like other medical therapies for other chronic medical illnesses, with no prior authorizations, dose limits, or time limits. Comprehensive addiction treatment includes detoxification, rehabilitation counseling, full medical and psychiatric assessment, continuing care, psychosocial assessment, 12-step and supportive recovery, and MAT. Among the most useful psychosocial therapy modalities are cognitive behavioral therapy (CBT), dialectical behavioral therapy (DBT), motivation-enhanced therapy (MET), aversion, and cue exposure. We need more efficacy studies of MAT with psychosocial therapies over longer periods of time.

- MAT for addiction should be treated like other medical therapies for other chronic medical illnesses, with no prior authorizations, dose limits, or time limits.
- Comprehensive addiction treatment includes detoxification, rehabilitation counseling, full medical and psychiatric assessment, continuing care, psychosocial assessment, 12-step and supportive recovery, and MAT.
- Food and Drug Administration (FDA)-approved MAT includes medications for detoxification, maintenance, psychiatric illnesses, and medical management of pain.
- Medications for detoxification include:
  - Librium (alcohol and benzodiazepine detoxification)
  - Benzodiazepine and phenobarbital (benzodiazepine detoxification)
  - Suboxone (buprenorphine and naloxone) and methadone (opiate detoxification)
  - Clonidine and naltrexone (opiate detoxification)
  - Bromocryptine and amantadine (stimulant detoxification)
  - Welbutrin (cannabis detoxification)
- Medications for maintenance include:
  - Buprenorphine and methadone (opiate dependence)
  - Acamprosate (alcohol dependence)
  - XR-NTX (Vivitrol) and oral naltrexone (alcohol and opiate dependence)
  - Disulfram (alcohol dependence)
  - Nicotine replacement (nicotine dependence)
- The psychosocial therapy approaches cited in the literature include those involving motivation to change, changing problem behaviors, contingency management, focus on factors on using problems, support counseling, treatment of family and partners, and the 12-step recovery approach.
- Among the most useful modalities are CBT, DBT, MET, aversion, and cue exposure.
- It is difficult to find efficacy studies for the combined use of MAT and psychosocial therapies. There are many studies that compare psychosocial therapies alone and MAT with different agents alone. The detoxification and psychotherapy studies show better outcomes than detoxification alone, and psychotherapy with continued use is shown to be futile.
- There are, however, some studies that examine the efficacy of MAT and psychotherapy:
  - In a double-blind, placebo-controlled, parallel-group study (Balldin et al., 2003), 118 patients with alcohol dependence were observed over 6 months. Each of four treatment groups received 50 mg of naltrexone or a placebo daily along with either CBT (nine sessions) or "usual care" supportive therapy. Results: The CBT-plus-naltrexone group had the longest mean period of abstinence before resuming heavy drinking.
  - Another study (O'Malley et al., 1995) examined 97 alcohol-dependent patients assigned to randomized groups that received naltrexone or a placebo and either coping skills therapy or supportive therapy for 12 weeks. Groups receiving naltrexone were less likely to exhibit heavy drinking through the first month of follow-up. The coping skills group with placebo also showed a decrease in drinking. Conclusion: Continued naltrexone therapy may be beneficial for some patients, and perhaps for all.
  - A third study (Carroll et al., 2001) assessed 127 patients in opioid detoxification in three randomized groups. Group 1 received naltrexone 3 days a week for 3 weeks; Group 2 received naltrexone with contingency management (CM) with vouchers;

and Group 3 got naltrexone with CM and significant other (SO) involvement. The naltrexone- with-CM group had more significant retention in treatment and reduced opioid use than the group that received naltrexone alone. The group that received naltrexone with CM and SO did not show greater retention or less substance use compared to the group that received naltrexone and CM. Conclusion: Behavioral therapies play a significant role in enhancing the utility of available pharmacotherapy.

- We need more studies MAT with psychosocial therapies with long-term experience—with 1-year, 2-year, and 5-year results.

Key points in the discussion following the two presentations on naltrexone overview and opportunities for psychosocial treatments:

- Counseling is useful, but should not be a barrier to patients receiving medication.
- We need to find better approaches for keeping people in treatment and improving long-term outcomes.
- Patients on XR-NTX also feel relief, but if they encounter stress, they are bereft because they are locked out of their coping method. The counselor must anticipate those needs, which are different for agonist and antagonist treatments; NIDA can help with models on how to do this.
- A study funded by NIDA and available online, "A Systematic Review on the Use of Psychosocial Interventions in Conjunction with Medications for the Treatment of Opioid Addiction," was released in the fall of 2015, and it includes a review of the literature.

Clinical Considerations

The next four presentations addressed provider issues and concerns related to non-agonist treatment for SUD.

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

Presenters: Joshua D. Lee, MD, MS, Associate Professor, Department of Population Health, New York University School of Medicine; Adam Bisaga, MD, Professor of Psychiatry, Columbia University of Physicians and Surgeons; and Richard Schottenfeld, MD, Professor of Psychiatry, Yale School of Medicine
(Conflict of interest disclosure: Dr. Bisaga received medication samples from Alkermes.)

Key points: A training program on Antagonist-based Treatment of Opioid Use Disorder in the Office Setting is being developed to help clinicians adopt naltrexone in their treatment of patients with OUD. An opioid antagonist, it attaches to the receptor and blocks other opioids from exerting any effects, leading to gradual extinction of craving and drug seeking. Treatment can be started only after a patient has been detoxified off opioids. Patients treated with XR-NTX have better treatment retention, lower opioid use, and lower craving as compared to those treated with a placebo. The primer discusses patient selection criteria, treatment initiation, maintenance treatment and treatment logistics, and considerations for use with special populations. Patients' informed and voluntary consent is critical.

- Training program on Antagonist-based Treatment of Opioid Use Disorder in the Office Setting is funded under the SAMHSA Providers' Clinical Support System for Medication-Assisted Treatment contract. It will be released to NIDA and used to train people with limited experience in treatment modalities.
- 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.
- The training consists of four sections (of which this presentation covers Sections 1–3):
  - Section 1: Introduction to Antagonist-based Treatment for OUD
  - Section 2: Patient Selection and Treatment Initiation
  - Section 3: Maintenance Treatment and Treatment Logistics
  - Section 4: Special Populations and Psychosocial Approaches
- Highlights from Section 1:
  - Antagonist-based treatment
    - Opioid antagonist attaches to the receptor; it has no intrinsic activity but it prevents other opioids from exerting any effects (receptor blocker).
    - 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.
    - Naltrexone is an appealing choice for patients seeking detoxification from all opioids as a first stage of treatment.
  - Naltrexone treatment: Mechanism
    - Behavioral component: Blockade of the positive (reinforcing) effects of heroin leads to gradual extinction of drug seeking and craving.
      - Patients who use while on naltrexone experience no effect and stop using.
    - Pharmacological component: Naltrexone decreases reactivity to drug-conditioned cues and decreases craving, thereby minimizing pathological responses contributing to relapse.
      - Patients on naltrexone usually have little to no urge to use.
    - As naltrexone has a different mechanism of action from agonists, it may address limitations related to treatment with agonists, thus attracting and benefiting more patients.
  - Antagonist-based treatment: Limitations
    - Detoxification and a wait period of 7–10 days after the last dose of an opioid are required before antagonist can be initiated.
      - These requirements can be a major barrier for many patients who find it difficult to tolerate withdrawal.
      - The reduction of inpatient/residential treatment programs is a further complication.
    - There may be difficulty with the induction due to the possibility of precipitated or protracted withdrawal.

        - Patients may not be feeling well at the beginning of the treatment.
        - Treatment requires close monitoring.
    - 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 the extended-release preparation.
        - Treatment should include an emphasis on adherence.
    - Patients treated with XR-NTX have better treatment retention, lower opioid use, and lower craving as compared to those treated with a placebo.
    - The majority of patients retained in treatment with XR-NTX have no or little concurrent opioid use.
    - XR-NTX is a relatively new drug, with few studies to date.
        - There is no direct evidence available yet comparing the efficacy of XR-NTX vs. buprenorphine.
        - Indirect comparisons show comparable treatment retention with a lower level of ongoing opioid use associated with XR-NTX.
- Section 2 points on patient selection and treatment initiation:
    - Informed and voluntary consent to XR-NTX treatment is critical.
    - Patients best suited for XR-NTX treatment include:
        - Those highly motivated to abstain from all opioids
        - Those in professions where agonist treatment is controversial
        - Those detoxified but at risk of relapse
        - Those who failed treatment with agonist
        - Those with a short history or lower level of opioid use
        - Young adults
        - Individuals who use opioids irregularly
        - Patients who want to discontinue agonist treatment without risk of relapse
    - Regarding treatment initiation, consider that XR-NTX is an opioid receptor antagonist, and treatment can be started only after a patient has been detoxified off opioids.
        - For patients still physically dependent or with heroin in their systems, XR-NTX will displace heroin from the receptor and terminate its effects, causing severe withdrawal.
        - To minimize risk, clinicians must confirm there is no physical dependence. If unsure, consider using the naloxone challenge or administer a test dose of oral naltrexone; if the oral naltrexone is tolerated, then give XR-NTX to the patient.
- Section 3 key points on maintenance treatment and treatment logistics:
    - It is expected that one-third of the patients will "test" the blockade within 1–2 days after starting XR-NTX treatment; most patients will "test" the blockade once or twice during the first week with small amounts of opioid to ensure the blockade is working. Some people will use large amounts of opioid within 1–3 weeks, but few persist, and very few will try to intentionally "override the blockade."
    - Another concern covered in this section is managing relapse. Some patients have increased cravings and may use within 3–4 weeks of treatment; often the first sign of relapse is missing a dose of XR-NTX.

- Managing severe pain, safety concerns, and the controversies surrounding antagonist-based treatment (depression and overdose) are also covered.
- Section 3 looks at treatment termination. The research shows that patients who receive XR-NTX for 6–12 months are more likely to experience full remission and abstinence from opioid use as compared to people who receive fewer doses.

Key points in the discussion following this presentation:

- Studies suggest XR-NTX has superior outcomes to oral naltrexone. Though "fail first" protocols call for prescribing XR-NTX only after oral naltrexone failure, no studies have examined these types of stepped-care algorithms for the different naltrexone formulations.
- Some payers want patients to be prescribed oral naltrexone first because it is less expensive than the injectable form of the drug. This is a practical and important patient-centered consideration; however, the risk of treatment failure and the evidence indicates this is an inferior strategy for opioid relapse prevention, and the risk of overdose is unacceptably high.
- A 6-month treatment study with an 18-month total follow-up period (Lee et al., 2016) showed lower rates of opioid relapse among outpatient criminal justice-involved volunteers treated with Vivitrol. Participants in this trial received basic medical management therapy consistent with general office-based provider-patient opioid education and adherence counseling.
- Patients completing detoxification can benefit from naltrexone because it may prevent them from relapsing.
- There is a serious need to address the pain threshold and the need for opioid analgesia for people on agonists vs. non-agonists. Some providers do not exclude people with chronic pain from treatment with naltrexone. Some patients continue to experience pain when on opiates, and naltrexone might be useful for those patients to have better pain control.
- There is concern about patients with various illnesses, such as liver disease and gastrointestinal illness, being put on naltrexone, but experts did not consider this to be a contraindication.
- Even though there are instructions in the package insert about how to inject the drug, there are many questions about how to administer XR-NTX. There is need for a centralized place for providers to access training materials and to have their concerns addressed.
- Providers get confused about how to administer naltrexone because it is the only injectable medication for OUD. In addition, to inject the medication into the buttock of someone of the opposite sex, a chaperone must be present.
- Checklists can help providers better understand how to receive, store, and inject the medication.
- It is important to make sure patients understand all of the risks associated with taking naltrexone. Participants felt patients should sign a treatment agreement that includes information on naltrexone as well as other medications administered to treat OUD.
- In the interest of shared decision making, it would be useful for SAMHSA to create an electronic template to inform patients about the risks and benefits of different forms of MAT, one that doctors can adapt to use for their specific needs.
- There is still some misunderstanding about which medications naltrexone cannot be used with, when the patient is ready to take the drug after detox, and the frequency and duration of XR-NTX administration.

Detoxification Protocols Compatible with Naltrexone Initiation

Presenter: Pamela J. Shultz, MD, FASM, Hazelden Betty Ford Foundation, Center City, Minnesota
(Conflict of interest disclosure: None reported.)

Key points: The protocol for the Hazelden Betty Ford Foundation (HBFF) 30-day residential detox program is an ideal, but it depends on many factors, including insurance, XR-NTX availability, and the patient's ability to tolerate discomfort and cravings. A variety of other protocols are also possible, both for inpatient and outpatient initiation of XR-NTX.

Indications for XR-NTX include concomitant use of opioids and other substances such as alcohol, history of noncompliance with oral medications, and severe OUD with a long history of intravenous use. Contraindications include pregnancy or unwillingness to avoid pregnancy, being under 18 years of age, LFT results greater than three times the normal range, anticipated acute pain in the near future (e.g., elective surgery), ongoing chronic pain that is only controlled with narcotic analgesic, and morbid obesity (which may make injection difficult).

- The protocol for the HBFF residential detox program is as follows:
  - Day 0: Admit patient to residential treatment
  - Days 1–2: Begin detox with buprenorphine/naloxone
  - Days 5–10: Buprenorphine/naloxone taper (individualized, depending on use history)
  - Wait 7–10 days: Ancillary medications only, then oral naltrexone, 25 mg x 1 day
  - Then oral naltrexone, 50 mg x 1 day
  - Next day, if oral tolerated, XR-NTX 380 mg intramuscular (IM)
  - Day 30: Discharge
- This is the ideal protocol if the patient is in residential and staying 28–30 days.
- Options for treatment of OUDs are discussed with the patient, including risks and benefits. The above method for detox and initiation of XR-NTX does not always work because it is based on the patient's decision and when the patient makes it.
- HBFF provides adjunct medications for detox, administered as either oral tablets or patches, which include hydroxyzine, docusate sodium, baclofen, dicyclomine, ibuprofen, catapres patches, and oral clonidine.
- Alternative protocols used to detox and initiate inpatients include:
  - Quicker taper off buprenorphine
  - Shorter wait before oral naltrexone and start at 6.25 or 12.5 mg per day
  - XR-NTX given after stepping down to outpatient
  - Off-label protocol using tramadol to help with withdrawal and to shorten wait before XR-NTX
- Outpatient induction:
  - Many patients do not tolerate being off opiates for 7–10 days; they may do better with low-dose buprenorphine and taper over several weeks.
  - Before the XR-NTX shot, HBFF administers a point-of-care urine drug screening, which includes tests for buprenorphine and fentanyl; a pregnancy test; and, if there's any question about recent use, an oral challenge with 50 mg of naltrexone and then patient observation for 1 hour.

- Comprehensive Opioid Response with 12-steps (COR-12™) was started at HBFF Center City campus in January 2013 to treat patients with OUD, integrating 12-step facilitation and other psychosocial treatments with medication in support of recovery.
  - The program has three tracks (three options): no medication (about 40 percent of patients), buprenorphine (about 20 percent), and XR-NTX (about 40 percent).
  - Compared to patients not in the COR-12 program, patients in the program are more likely to be males and be younger, to stay in residential treatment longer, and to step down to outpatient.
  - Atypical discharges were significantly reduced in COR-12 program participants, and there was no difference in atypical discharges between the three COR-12 tracks.

Key points in the discussion following this presentation:

- Many patients are not on MAT at HBFF as they go into 12-step programs, whereas in private practice 90 percent of patients are on medication. HBFF would like to see more patients opt for MAT, but some do not want to commit to long-term programs, many do not want to stay in Minnesota for long term-treatment, and some insurance companies will not pay for the treatment for the long term. They are encouraged to continue some other treatment.
- The 12-step medication recovery work, through which people in stable recovery provide support to others undertaking recovery, should perhaps be a recommended practice. They can tell others about using Vivitrol, tapering off meds altogether, or other options.
- There is a problem with people in 12-step programs telling others how to treat their disease. There should be a mandate for training on evidence-based practice: people need to be given a choice.
- Some providers are working with sober houses to get them to accept people on MAT.

Preventing and Reducing Overdose Including Education for Patients and Clinicians

Presenter: Joshua D. Lee, MD, MS, Associate Professor, Department of Population Health, New York University School of Medicine
(Conflict of interest disclosure: None reported.)

Key points: Patients should be advised that any opioid use is dangerous. Overdose prevention counseling should be offered to all patients with OUDs and those receiving opioid analgesia. It appears overdose events will always accompany opioid use, including use by individuals who are or recently have been in treatment with XR-NTX, and sometimes overdose will be fatal. Dropout and relapse will happen, and clinicians should reach out in particular to patients who have recently missed a scheduled monthly injection. Overdose prevention involves counseling related to predispositions (e.g., use of prescription opioids, polypharmacy) and safe use, as well as providing Narcan and encouraging training in basic cardiopulmonary resuscitation (CPR), including rescue breathing, to all opioid users.

- MAT—with medications such as buprenorphine, methadone, and XR-NXT—likely yields lower overdose rates vs. out-of-treatment or counseling-only treatment, but more definitive data are needed.
- People should be advised that any opioid use is dangerous, and they should be counseled about preventing overdose, both during and after MAT.

- People who are in treatment with XR-NTX, or recently have been in treatment, will sometimes overdose and will sometimes fatally overdose.
- In a recent criminal justice-focused randomized-control trial (RCT), the Kaplan-Meier Curves for Relapse-free Survival showed that the probability of relapse-free survival for patients on XR-NTX was higher than for patients who received treatment as usual (TAU) (Lee et al., 2016).
- In this same study, at the end of a 6-month treatment phase, no XR-NTX participants continued XR-NTX therapy; by 12 and 18 months from baseline, rates of self-reported opioid use and positive opioid urine samples were similar between the two arms. This indicated that treatment discontinuation ended a period of benefit and risk reduction. Opioid use rates resumed in about 20 percent of XR-NTX participants previously abstinent when on XR-NTX.
- No overdose events were observed among XR-NTX participants through 18 months vs. 7 events ($p=0.02$) among TAU participants. This included during the immediate post-treatment weeks among XR-NTX participants ending treatment early, at the 6-to 7-month period (after the six scheduled monthly injections), and during a rise in self-reported opioid use rates among previously abstinent XR-NTX participants in months 6–18.
- While a secondary outcome to be interpreted with caution from a large RCT focusing on 6-month relapse prevention, these overdose findings were reassuring: there was no signal of excess or usual rates of overdose among XR-NTX participants during, immediately after, or long after active therapy. Staff should track and prevent dropout by monitoring active vs. passive follow-ups to keep patients on schedule. Staff should also monitor missed injections (which should trigger increased outreach).
- The highest risk for overdose is generally thought to be in the 4 weeks post-XR-NTX injection, or thereafter whenever opioid use resumes (whenever an individual with low tolerance and no antagonist blockade resumes opioid use)
- The use of illicit fentanyl has increased recently and likely implies a higher risk of overdose. Clinicians should receive training about this increase, and patients need counseling about the effects of the drug.
- Predispositions to overdose include the use of prescription opioids, heroin, and illicit fentanyl; polypharmacy use, such as benzodiazepines, alcohol, and stimulants; and other factors, such as recently being in a controlled environment, switching pain medications and duration, chronic obstructive pulmonary disease (COPD), and sleep apnea.
- For overdose prevention, all opioid users should receive counseling, naloxone, and CPR training, including rescue breathing.
- In an 8-week pilot proof-of-concept RCT of XR-NTX given before release from jail in NYC (Lee et al., 2015), 34 patients received a first shot just prior to jail release and one shot a month later. The data showed no overdoses in either arm post-release. While this small trial did not show differences in overdose rates, the application of MAT including XR-NTX to clinical scenarios when overdose is more likely (e.g., release from a controlled environment) warrants further study as a specific overdose prevention intervention.

Emerging Therapies

Presenter: Charles Gorodetzky, MD, PhD, Consultant to US WorldMeds
(Conflict of interest disclosure: Dr. Gorodetzky has consulted with US WorldMeds on the development of lofexidine.)

Key points: Alpha-2 adrenergic agonists, such as clonidine and lofexidine, are effective in alleviating the symptoms of acute opioid withdrawal. In recent clinical trials in the United States, lofexidine has been shown to be safe and effective. It may also be useful in preventing relapse and in transitioning patients to total withdrawal from medication.

- The use of alpha-2 adrenergic agonists to alleviate the symptoms of acute opioid withdrawal is not a new concept. Many withdrawal symptoms and signs are due to adrenergic hyperactivity, and alpha-2 agonists antagonize this general adrenergic activity. Therefore, it was proposed in 1980 that such drugs could be useful in alleviating some of the symptoms of opioid withdrawal. The drug chosen to test this hypothesis was clonidine (an approved antihypertensive medication), which did show efficacy and has been used off-label since.
- Gowing et al. have been reviewing the use of alpha-2 adrenergic agonists for the treatment of opioid withdrawal since 2001. Their most recent review was published in 2014. The group reviewed studies on four drugs: clonidine, lofexidine, guanfacine, and tizanidine (Gowing et al., 2016). They reviewed 3,500 publications and analyzed 26 trials including 1,668 participants, focusing on the efficacy and safety of the drugs. Of the 26 trials, 5 compared the drugs to placebo, 12 compared the drugs to methadone, 5 compared clonidine to lofexidine, and 4 compared alpha-2 adrenergic agonists to other types of treatment.
- Clonidine and lofexidine were found to be clearly more effective than placebo in reducing withdrawal symptoms, and patients were more likely to complete detox on these two drugs. Methadone was marginally more effective than clonidine and lofexidine; there was no difference between clonidine and lofexidine; and clonidine was found to be more effective than the other treatments for withdrawal that were reviewed.
- The research showed that there is a greater incidence of hypotension as a side effect with alpha-2 agonists than other treatments.
- Lofexidine will probably be the next drug available in the United States to treat opioid withdrawal. It is a structural analog of clonidine, which was developed in the late 70s/early 80s as an antihypertensive medication. It was approved and has been marketed for alleviation of opioid withdrawal in the United Kingdom since 1992 and is estimated to have been used in more than 250,000 withdrawals.
- The U.S. Investigational New Drug (IND) application was filed in 1995, and lofexidine is currently under development for the opioid withdrawal indication by US WorldMeds, Louisville, Kentucky. Approximately 15 Phase 1 and Phase 2 studies have been completed, as well as 3 double-blind, placebo-controlled efficacy/safety studies. In all studies, lofexidine has been shown to be more effective than placebo in alleviation of the symptoms of opioid withdrawal and resulting in a higher proportion of patients completing the medically supervised withdrawal.
- The overall safety and tolerability has been very good. Primary side effects of concern are hypotension and bradycardia, which have not appeared to be major clinical problems in the clinical trials. There is also detectable rebound hypertension when the lofexidine is discontinued, but again this has not been a clinical problem.

- The studies reviewed by the Gowing et al. did not see any safety alerts in regard to patients on methadone. Only one person has died as a result of using lofexidine in combination with another drug.
- US WorldMeds has done specific interaction studies with lofexidine administration in combination with methadone, buprenorphine, and naltrexone and has not found any significant safety problems, including, specifically with QTc prolongation.
- Lofexidine may be useful in relapse prevention. Researchers are currently looking at studies of this effect and of other drugs to prevent stress-induced relapse.
- Lofexidine may also be useful in transitioning from an opioid agonist to naltrexone or buprenorphine, reduction in maintenance dose of methadone or buprenorphine, as well as in totally withdrawing a patient from maintenance medication.

Patient Population Considerations

The next six presentations concerned patient-centered care and decision-making and treatment for particular patient populations**.**

Patient Choice and Individualized Treatment

Presenter: Robert Schwartz, MD, Friends Research Institute
(Conflict of interest disclosure: Dr. Schwartz provided a one-time consultation to Reckitt Benckiser on behalf of Friends Research Institute.)

Key points: Patients choose their treatment for OUD based on information available to them via publications, Internet, and word of mouth. Their considerations in choosing treatment include personal values, risk aversion, experiences with treatment, cost, access, and family preferences. To help patients make better choices and help professionals personalize patient treatment and care, we need more research data, physician decision aids, patient decision aids, and equal access to all FDA-approved medications and treatment.

- Patients choose their treatment based on information available to them via publications, Internet, and word of mouth. Their considerations including personal values, risk aversion, experiences with treatment, cost, access, and family preferences.
- There is still uncertainty about which type of treatment is best for which type of patient, and response to treatment cannot be predicted based on patient characteristics (Krupitsky et al., 2011a, 2011b).
- One provider's blog (D. Sack, n.d.), an example of what is found on the Web, talks about naltrexone myths: that it is not that effective, it's hard to remain on treatment, it's just another drug to abuse, it is too expensive, and it has too many side effects. A provider's website talks about methadone treatment as a "prison."
- The personal values that patients consider when deciding about which treatment to choose include their desire to take a medication, a belief that pharmacotherapy is not recovery, aversion to opioid medications, and patient preference for personal autonomy vs. structure in treatment.

- Patients' prior treatment experiences, along with experiences of untreated opioid withdrawal (for arrested methadone patients: Maradiaga et al., 2016; Mitchell et al., 2009) and medication side effects (Peterson et al., 2010).
- Financial considerations include insurance coverage, out-of-pocket expenses, and grant-funded treatment. Cost may be a determining factor in the patient's decision to start and stay in treatment (Booth et al., 2003).
- Access is another element in a patient's decisions about treatment, factors being locality, waiting lists (Schwartz et al., 2006), travel burden (Greenfield et al., 1996), appointment flexibility, and confusion about where to get the kind of treatment desired. Ideally, there would be a central referral source that does not represent a particular type of approach.
- Family preference for one type of treatment over another plays a role in a patient's decision about treatment, as do negative attitudes associated with some forms of treatment, such as methadone.
- There are limited data regarding the benefit of inpatient rehabilitation (e.g., 28-day programs) compared to outpatient treatment. There are also limited data regarding additional benefits of intensive vs. standard outpatient treatment when combined with buprenorphine (Mitchell et al., 2013). Random assignment studies to date indicate that adding counseling to medication management may not confers additional benefit when combined with office-based buprenorphine treatment (Fiellin et al., 2006; Weiss et al., 2011).
- To help patients make better choices and help professionals personalize patient treatment and care, the field needs more research data, physician decision aids, patient decision aids, and equal access to all FDA-approved medications and treatment.
- Some general decision-making tools outside of the addiction field include *Evidence-based Clinical Decision Making* by Haynes, Devereaux, and Guvatt (2002) and *Shared Decision Making* by O'Connor et al. (2007).
- The approach outlined by Friedman (2016) appears useful in a medication scorecard is provided to patients with the cost, numbers needed to treat, and the number of positive and negative clinical trials for each medication.

Extended-release Naltrexone for Persons Living with HIV with Opioid and Alcohol Use Disorders

Presenter: Sandra Springer, MD, Associate Professor of Medicine, Department of Internal Medicine, Section of Infection Disease, Yale School of Medicine
(Conflict of interest disclosure: None reported.)

Key points: For people living with HIV (PLH), effects of drug use include increased sexual risk and injection drug user (IDU) risk behaviors, reduced adherence to antiretroviral therapy (ART), and increase in HIV viral load (VL) and the progression to AIDS. Preliminary evidence suggests that XR-NTX may prevent relapse to opioids for PLH upon release from criminal justice settings and that XR-NTX may help maintain or improve HIV VL suppression. Comorbid cocaine use among those with OUD or alcohol use disorder (AUD) negatively impacts retention on XR-NTX.

- The effects of drug use on the HIV continuum of care include increased sexual and IDU-related risk behavior, increased acquisition and transmission of HIV, reduced ART adherence, and increase in HIV VL and the progression to AIDS.
- The Joint United Nations Programme on HIV/AIDS (UNAIDS) plan is to end AIDS by 2030. Its goals are that, by 2020, 90 percent of people who are HIV-positive will know they have the disease, 90 percent of those aware of their status will receive ART, and 90 percent of those receiving AIDS-related treatment will have VL suppression. These goals cannot be accomplished without paying attention to persons who use drugs and alcohol.
- Research conducted in 2004 looked at HIV treatment outcomes among PLH during incarceration and after release to the community in the state of Connecticut and found that HIV VL suppression, high at time of release, was lost within 3 months after release to the community (Springer et al., 2004). Reasons for loss of viral suppression are considered multiple but include relapse to drug and alcohol use, insufficient access to medication refill centers, under-treatment of mental illness, lack of supervised care and social instability, and lack of Medicaid or a need to re-enroll (Springer et al., 2011).
- Springer and colleagues published the acceptability and methods (2014) of a double-blind, randomized, placebo-controlled trial of XR-NTX for alcohol-dependent and hazardous-drinking prisoners with HIV who were transitioning to the community, testing whether, when compared with placebo, XR-NTX would maintain/improve the proportion with VL suppression and whether XR-NTX would improve alcohol treatment outcomes. Participants received a naltrexone injection pre-release and five more injections post- release (Springer et al., 2014). Preliminary findings showed that XR-NTX was statistically significantly associated with maintaining or improving HIV VL suppression as compared to the placebo group 6 months after release (Springer et al., 2016b). In addition, time to heavy drinking day after release among those aged 21–29 years was statistically significantly longer as compared to the age-matched placebo group (Springer et al., 2016a).
- A second study recently conducted by Springer and colleagues utilized a double-blind, randomized, placebo-controlled trial of XR-NTX for HIV-infected, opioid-dependent prisoners and jail detainees transitioning back to the community. Methods and initial acceptability and implementation issues were previously published (Di Paola et al., 2014). Preliminary findings reported but yet published or finalized, showed that those who received XR-NTX had a higher rate of VL suppression at 3 months as compared to the placebo group.
- When Springer and colleagues looked at both studies combined in an earlier analysis to assess retention on study treatment within 1 month after release to the community, cocaine use was found to be the main cause of people not returning for the second injection of naltrexone, their first injection after release to the community. Overall, however, they found that XR-NTX is accepted by PLH and those within criminal justice system (CJS) settings. XR-NTX may be a feasible conduit to care for PLH with opioid and alcohol use disorders as they transition to the community, even those with severe psychosocial disparities as both populations including high rates of homelessness, comorbid SUD other than AUD and OUD, mental illness, and high proportions of racial and ethnic minorities. XR-NTX is safe, without major hepatic adverse events, as Springer and colleagues also have previously analyzed in a combination of the two studies (Vagenas et al., 2014), again where the population was all PLH on ART with high rates of comorbid hepatitis C virus (HCV) and mental illness.
- Conclusions: Preliminary evidence suggests that XR-NTX may prevent relapse to opioids and alcohol for PLH upon release from CJS and that XR-NTX may help maintain HIV VL

suppression or improve VL suppression after release to the community. Comorbid cocaine use negatively impacts retention on XR-NTX among PLH with OUD and/or AUD released from CJS. XR-NTX is safe and does not cause serious hepatic dysfunction or other serious adverse events among PLH.

American Indian and Alaska Natives: Patient Population Considerations

Presenter: Alec Thundercloud, MD, Director, Office of Clinical and Preventive Services, Indian Health Services
(Conflict of interest disclosure: None reported.)

Key points: Death rates for American Indians and Alaska Natives (AI/AN) from many causes are higher than those of non-Natives, and the AI/AN drug-related death rate has risen 454 percent since 1979–1981. Often tribal communities lack the infrastructure required for the coordination that is essential for effective SUD treatment, and AI/AN may be referred to services that are not culturally appropriate or are far away from families and aftercare. Strategies to improve care include improving access to aftercare programs and transitional living facilities for youth returning after residential treatment, exploring community-based relapse prevention activities, and partnering with federal agencies to improve coordination, as well as supporting providers with mandatory opioid training for Indian Health Service's (IHS) prescribers of treatment medications, no-cost buprenorphine training toward getting waivered, and IHS teleECHO clinical support.

- Native American children are growing up facing more than one adverse childhood experience, coupled with historical trauma, which increases their risk of negative coping behaviors such as substance use.
- The death rates for AI/AN were higher than those of all other races in 2008: from suicide, 60 percent greater; related to alcohol, 520 percent greater; from motor vehicle crashes, 207 percent greater; from unintentional injuries, 141 percent greater; and from homicide, 86 percent greater.
- More than one-third of AI/AN live in poverty, fewer have high school or equivalent diplomas or Bachelor’s degrees, and their labor force participation is lower than that of the general population.
- There are great disparities in physical and mental health rates; deaths from diabetes, chronic liver disease, and cirrhosis are 40 percent higher than in the general U.S. population; and the suicide rate is 3–6 times higher among AI/AN than among their non-Native peers.
- The age-specific drug-related death rate for AI/AN males peaked at 51.8 percent for males aged 35–44 years old. The highest age-specific rate for AI/AN females (44.0 percent) occurred in the 45–54 age group. These AI/AN rates have been adjusted to compensate for misreporting of AI/AN race on state death certificates.
- The age-adjusted AI/AN drug-related death rate was 4.1 deaths in 2007–2009 was 22.7 per 100,000 people, a 454 percent increase from the rate of 4.1 deaths per 100,000 in 1979–1981.
- Coordination of services is essential, but in tribal communities the infrastructure needed for this coordination may be missing. Often when AI/AN patients are referred to services, they may be referred to a system outside their home community that is not tailored to provide culturally relevant services.

- IHS funds a total of 13 Youth Regional Treatment Centers (YRTCs), and 11 of those are fully constructed and either accept patients or are finishing the final preparation to begin accepting patients. YRTCs are tailored to include culturally relevant services and interventions, but they are often located long distances from families, support services, and aftercare, which becomes an issue at discharge.
- Ways to improve the continuum of care include increasing access to aftercare programs and transitional living facilities for youth returning to the communities after residential treatment, exploring approaches to engage community-based relapse prevention activities, and partnering with federal agencies to improve coordination at the local and national levels.
- Other strategies to improve care include mandatory opioid training for all IHS prescribers of treatment medications; no-cost buprenorphine training, funded by SAMHSA, toward getting waivered; and IHS teleECHO clinical support for providers.
- Promising practices with naloxone include a tribal health program partnership with IHS to provide Vivitrol in Red Rock, Minnesota; a tribal program of the Ho-Chunk Nation in Wisconsin that utilizes multidisciplinary teams for an integrated, patient-centered approach; an IHS co-prescribing initiative for opioid overdose prevention with naloxone; and a program training Bureau of Indian Affairs officers to administer and store naloxone.
- The extended family—the central organizing unit of many AI/AN cultures, emphasizing interdependence, reciprocity, and obligation of care for one another—functions as a protective factor.

Naltrexone in Pregnancy

Presenter: Elisabeth Johnson, PhD, NP, Director of Health Services UNC Horizons Program; Assistant Professor, Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill
(Conflict of interest disclosure: None reported.)

Key points: Because there are no adequate and well-controlled studies on pregnant women, naltrexone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are unresolved issues around inducting pregnant women onto naltrexone, handling the stress of withdrawal on the woman and the fetus, the fact that naltrexone precludes the use of opioid for pain relief and may make women more sensitive to pain, and the ways it may affect ability to breastfeed (possible reduced milk production, effects of medication consumed via breast milk on the neonate). Shared decision-making concerning naltrexone treatment for women with opioid dependence is required before pregnancy, at conception, in all three trimesters, and postpartum, weighing risks and benefits for mother and child. Research on the risks and benefits for this patient population is urgently needed.

- The FDA has classified naltrexone in Pregnancy Category C, which means there is little information about its impact on pregnancy. The drug has been shown to increase the incidence of early fetal loss when given to rats at doses 5 times the recommended therapeutic dose, and to rabbits at doses 18 times the recommended dose.
- Because there are no adequate and well-controlled studies on pregnant women, naltrexone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- The expected advantages of prescribing pregnant women naltrexone include the lack of psychosocial effect and misuse potential; birth outcomes within normal limits (per data from an Australian study); and low to normal neonatal abstinence syndrome/neonatal opioid withdrawal.
- Human research has been limited to an extremely small number of cases (25) followed after maternal treatment with oral or XR-NTX of varying lengths. Neonatal outcomes were unremarkable in these studies, and many questions remain about children born to mothers using naltrexone, such as the extent to which the medication alters pain sensitivity, respiration, response to stress and/or emotional responses, and susceptibility to the pain-relieving and addiction-related effects of opioids.
- The 25 published Australian cases of prenatal exposure to implanted naltrexone compared outcomes for prenatally naltrexone-exposed neonates to a historical sample of prenatally methadone-exposed neonates. As an opioid antagonist, rather than an opioid agonist such as buprenorphine, naltrexone does not produce neonatal abstinence syndrome (NAS).
- An initial survey of 58 pregnant women enrolled in a methadone maintenance treatment program found they were interested in learning about naltrexone because it would not give them the same mental fogginess or withdrawal symptoms they got from methadone. The women were concerned about naltrexone's effects on pain medications they might receive during labor and after a C-section and its effects on breastfeeding. These results point to the importance of having more options to offer pregnant women for treatment.
- Shared decision-making concerning naltrexone for the treatment of women with opioid dependence is required before pregnancy, at conception, in all three trimesters, and postpartum. It requires weighing risks and benefits for mother and child of naltrexone vs. no treatment, beginning treatment, continuing treatment, and switching to an opioid agonist medication.
- Practitioners often have little or no experience treating pregnant women. There are unresolved issues around how best to induct pregnant women onto naltrexone; how to handle the stress of withdrawal on the woman and the fetus; the fact that naltrexone precludes the use of opioid for pain relief and may make women more sensitive to pain; and the ability to breastfeed due to possible reduced milk production and the effects of medication consumed via breast milk on the neonate.
- Women who are in treatment for OUD with naltrexone may become pregnant, and we need to know how to take care of them and offer them options.
- Pregnant women with OUD should have medication options to choose from as a part of a comprehensive treatment program.
- Early and careful testing of naltrexone may provide data that minimize mass harm before mass exposure occurs or provide safety and efficacy data to allow pregnant women to benefit from medical advances as with larger populations.
- Research on the risks and benefits of naltrexone in this patient population is urgently needed.

Special Populations: Adolescents and Young Adults

Presenter: Marc J. Fishman, MD, Assistant Professor, Psychiatry and Behavioral Sciences, Johns Hopkins University; Medical Director, Mountain Manor/Maryland Treatment Centers
(Conflict of interest disclosure: Advisory board or committee: US WorldMeds; consultation: Alkermes; equity holdings, governing board or officer, and salary: Maryland Treatment Centers.)

Key points: Treating adolescents and young adults with XR-NTX brings some special challenges. Response to relapse prevention medication, including both XR-NTX and buprenorphine, is promising, but outcomes are generally not as good as in adults. Barriers to youth treatment may include developmental challenges such as impulsiveness, feeling invincible, resisting the burdens of treatment, pushing back against parental involvement seen by them as "intrusive," medication non-adherence, and continued use of other substances, especially cannabis. There is very high psychiatric comorbidity in this population. Getting parents involved may present challenges too, partly due to privacy issues. There is a need for residential inpatient treatment and preparation of young people for leaving a residential facility. A "family framework" with simple guidelines is needed when the young people enter treatment and after, spelling out role definitions, expectations, and responsibilities.

- The opioid epidemic has had catastrophic consequences for adolescents and young adults and their families. Young adults in particular are disproportionately affected, with the highest prevalence across the lifespan for use of prescription opioids and heroin. The tragedy of youth overdose and death has affected every community across the country. Unfortunately there are very few youth-specific programs, and treatment capacity for this population is underdeveloped. There are concerns about how best to serve this population for OUD, and there is no clear consensus about treatment approaches.
- There is a very high incidence of psychiatric comorbidity in this population. Psychiatric severity seems to make engagement difficult and drive relapse. Treatment of psychiatric comorbidity is an essential component of OUD treatment.
- There is a need for residential/ inpatient treatment. While some youth can effectively initiate treatment at an outpatient level of care, inpatient/residential treatment is often required to stabilize high-severity youth in crisis who are initially too chaotic to engage in outpatient treatment. This type of treatment is not curative but a first step, and residential treatment should prepare people young individuals for the next steps, including continued outpatient treatment after leaving the facility. Inpatient/residential treatment is an ideal setting for initiation of relapse prevention medication, including XR-NTX.
- In a case series reported by Fishman and colleagues (2010), of 20 youth who received a first dose of XR-NTX in residential treatment, 16 initiated outpatient treatment, and 10 were still in treatment after 4 months.
- A naturalistic study of young adults in Maryland (Vo et al., 2016) demonstrated practical feasibility and good outcomes under real-world, public-sector clinical conditions for patients who initiated treatment with either XR-NTX or buprenorphine in residential treatment, then continued in specialty outpatient for youth with opioid addiction. There were practical feasibility and patient acceptability for using both medications side by side in a mixed medication program in this population. At 6 months, there was about 40 percent retention in treatment. There were no significant differences in outcomes between patients on XR-NTX and buprenorphine, though early on, those on XR-NTX seemed to do better before the difference attenuated around weeks 8–10 of outpatient treatment.
- Young people often drift in and out of treatment and do not seem to be as motivated by withdrawal to stay in treatment as adults are. Young people need a lot of structure, but they often resist structure and the other burdens of treatment, which may limit retention.

- Another concern is continued use of other non-opioid substances. In particular, use of marijuana and alcohol is very prevalent. Youth often don't see cannabis as a problem, especially in the context of decriminalization, legalization, and "medical marijuana." Although it seems likely that ongoing use of other substances leads to worse outcomes, how to approach this most effectively remains puzzling..
- It can be difficult to get parents involved in treatment and to give them information because of privacy and confidentiality issues. Although parental involvement and supportive parent intervention are usually helpful, adolescents and young adults may resist because of developmentally normative striving for autonomy, prematurely seeing themselves as independent, pushing back against parental concern that they may see as intrusive and restrictive. Parents may also abdicate responsibility.
- A "family framework" with simple guidelines is needed when young people enter treatment, spelling out role definitions, expectations, and responsibilities. It should address family conflict, the transparency of information, backup plans, and what happens when things are not working out as anticipated. Parents may have a uniquely helpful role in supporting medication adherence, as in organizing and monitoring the return for ongoing XR-NTX injections/treatment.
- A future direction may include home delivery of naltrexone for continuing care following initial inpatient induction. In our ongoing preliminary pilot of XR-NTX home delivery, several remained in treatment over a 4-month period.

Individuals with Co-occurring Disorders: Naltrexone and Comorbid Conditions

Paolo Mannelli, MD, Associate Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center
(Conflict of interest disclosure: Research funding from Orexo, Alkermes; advisory board, Alkermes.)

Key points: Studies have examined the effects of naltrexone to treat users of alcohol and other drugs, those with psychiatric comorbidity, and those with comorbid medical disorders. There is evidence that naltrexone reduces effects of and/or craving for cocaine and amphetamine. For the 6 in 10 people with SUD who also suffer mental illness, treating both/multiple illnesses at once in an integrated fashion generally leads to the best outcomes. When prescribing naltrexone, it is important to conduct a complete psychiatric evaluation and monitor mood and behavior during treatment to identify patients at risk of increased depression and adverse events of a suicidal nature and consider use of a combination treatment with appropriate medications. Trials have shown naltrexone is safe in treating patients with HIV/HCV, and obesity does not seem to affect the drug's efficacy (though the drug does not appear to facilitate weight loss). Naltrexone treatment is medically safe but requires medical clearance and monitoring of liver function

- Naltrexone and polydrug use. Clinical trials have been conducted for naltrexone use with alcohol plus cocaine, tobacco, and gambling, and with opioid plus cocaine, amphetamine, tobacco, and cannabis. Polydrug users may be good candidates for naltrexone treatment, and in general naltrexone use seems safe.

- Studies have shown that naltrexone reduces effects of and craving for cocaine and amphetamine; it has affected cannabis use, but the effect may dissipate over time; and it has had inconsistent impact on a person's urge to gamble.
- Several factors—including medication dosage, length of treatment, sample size, and attrition rate—limit the interpretation of findings. In Phase II trials, problems such as high dropout rates, missing data, and a lack of agreement on outcomes complicate efforts.
- Combination pharmacotherapy (e.g., disulfiram, varenecline, buprenorphine) is gaining interest.
- Higher dose, longer treatment duration, and XR-NTX use may be more likely associated with a positive outcome.
- Other areas of further study include co-occurring AUD and OUD, women, minorities, older users, and outcomes (e.g., heavy drinking vs. sobriety).
- Psychiatric comorbidity:
  - As many as 6 in 10 persons with an illicit SUD also suffer from mental illness, and rates are similar for users of licit drugs, such as tobacco and alcohol. Research indicates that treating both (or multiple) illnesses simultaneously in an integrated fashion generally leads to the best outcomes (NIDA, 2009).
  - Though literature reviews have warned of the existence of depression risk in SUD patients treated with naltrexone (Miotto et al., 1997; Ritter, 2002), follow-up studies have failed to associate naltrexone use with increased risk of depression (Miotto et al., 2002; Dean, 2006; Mysels et al., 2011).
  - For AUD patients, in controlled trials, adverse events of a suicidal nature and depression-related events were more common in patients treated with medication than with placebo (~1 percent vs. 0 percent in both cases). In AUD patients, adverse effects involving depressed mood were reported by 10 percent of XR-NTX-treated patients vs. 5 percent of placebo-treated patients (Alkermes, 2015).
  - In a long-term safety study, adverse events of a suicidal nature were reported by 5 percent of OUD patients treated with XR-NTX and 10 percent treated with oral naltrexone (Alkermes, 2015). The 24-week, OUD pivotal trial reported no adverse events involving depressed mood or suicidal thinking (Krupitsky et al., 2011).
  - Trials using naltrexone in SUD have included antidepressant medications to improve outcomes with inconsistent results, but it is not always clear whether patients had pre-existing depression and whether comorbidity affected treatment outcomes (Krupitsky et al., 2006; Farren & O'Malley, 2002; Pettinati et al., 2010, 2013; Adamson et al., 2015).
  - Current studies are looking at the antidepressant activity of naltrexone, alone or in combination with buprenorphine or antidepressants (Ehrich et al., 2015; Murphy et al., 2014).
  - It is important that providers conduct a complete psychiatric evaluation and monitor mood and behavior during treatment in order to identify patients at risk and decide on the use of a combination treatment with medications for depression. Safety has been determined for combinations with common antidepressants (selective serotonin reuptake inhibitors [SSRIs], bupropion, atypical).
  - Future developments should focus on the role of opioid system modulation in mood disorders.

- Medical Comorbidity:
  - Injecting and noninjecting drug users are at increased risk of HIV, HCV, and other infectious diseases. Effective drug use treatment includes HIV/HCV prevention because it reduces associated risk behaviors, such as sharing paraphernalia and engaging in unprotected sexual activity (NIDA, 2009).
  - Safety of naltrexone in clinical trials: 6-month LFTs were comparable in methadone- and oral naltrexone-treated HCV patients and lower than in patients enrolled in drug-free programs (Lozano Polo et al. 1997). Highly active antiretroviral therapy (HAART)-treated/nontreated OUD or AUD patients on XR-NTX or oral naltrexone and high HCV/psychiatric comorbidity have shown reversible LFTs elevation comparable to placebo-treated and non-HIV patients (Mitchell et al., 2012; Tetrault et al., 2012; Vagenas et al., 2014).
  - The role of the endogenous opiate system in regulating food intake and body weight has been long debated (Reid, 1985). There are no clear signs of that naltrexone facilitates human weight loss via a hedonic blockade (O'Brien et al., 2011), and early obesity trials were negative (Atkinson et al., 1985). Data of XR-NTX use in OUD patients have failed to show patient's body weight affects treatment efficacy (FDA, 2010). Naltrexone has shown inconsistent/gender-related ability (i.e., more pronounced in women) in controlling smoking cessation-related weight gain (Toll et al., 2010; King et al., 2012, 2013). A combination naltrexone/bupropion was recently approved for the treatment of obesity and has shown a favorable safety/abuse profile compared with existing treatments (Verpeunt & Bello, 2014).
  - Naltrexone treatment is medically safe, though it requires medical clearance and monitoring of liver function. There is not enough information on its safe use in the case of severe liver impairment.
  - Naltrexone is safe also for use in HIV/HCV patients and may gain an important role in limiting the spread of infectious diseases.
  - The collection of metabolic information in cohorts of patients treated with naltrexone may be instrumental in determining its role in controlling and reducing risk of metabolic disorders that is increasingly identified in (older) individuals with SUD (Virmani, 2007).

Key points in the discussion following the six presentations on patient population considerations:

- How do we allow for and pay for inpatient treatment/detox with XR-NTX? Private insurance generally pays for detox, and MAT can begin inpatient and then transition to outpatient. In Maryland, state and commercial insurance will pay for naltrexone for inpatient adolescents. Commercial payers that provide addiction treatment are required to pay for pharmacotherapy under the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA). Payers that do not provide such benefits should be encouraged to do so.
- Using pharmacies to deliver naltrexone to patients is a scalable strategy for treating people with the drug. The doctor would first see the patient and send the patient to the pharmacy to receive the drug. This option varies by state, however.
- Naltrexone could be offered at infusion centers, in the home, or at injection sites set up by providers, but there are many logistical issues that need to be worked out. Health parity law may be a way to address this issue.

Provider Considerations

The next four presentations were about issues providers need to consider related to XR-NTX: physicians working in underserved areas, non-physician providers, nonmedical stakeholders and individuals in controlled settings, and implementation models.

Cornerstone at Helping Up Mission Clinic

Presenter: Denis Goodwin Antoine, II, MD, Director, Motivated Behaviors Unit, Johns Hopkins Hospital, Assistant Professor of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine
(Conflict of interest disclosure: None reported.)

Key points: The Cornerstone clinic is a partnership between Baltimore's religious-based Helping Up Mission and Johns Hopkins University to treat homeless and near-homeless men with OUD who come to the mission. The clinic provides a treatment course which includes intensive outpatient treatment of SUDs, referral to emergency services, mental health, and medical care, and housing, providing an opportunity for a new cycle. The mission has a no-tolerance policy, and the clinic does not prescribe medication, but XR-NTX is used by about 18 percent of the men after referral to a primary care provider. Strengths of the program are proximity to the target population, low relapse rate, financial viability (100-percent Medicaid-funded), opportunities for clinical training, and a stable population for health services outcome data. This model demonstrates that academic and community partnerships are feasible and can literally "meet people where they are."

- Cornerstone at Helping Up Mission Clinic is a partnership with Johns Hopkins University in Baltimore, Maryland. The clinic houses homeless men and near-homeless men, most of whom have SUD. It is a therapeutic community/homeless shelter with religious-based classes and access to medical/mental health staff and volunteers who provide ancillary services, e.g., dental and ophthalmology.
- The clinic provides intensive outpatient psychotherapy that utilizes a combination of contingency management, motivational interviewing and cognitive behavioral therapies, and housing, providing an opportunity for a new cycle. The Mission has a no-tolerance policy that can be a barrier to treatment at times within the clinic. It does not directly prescribe medications, including buprenorphine or methadone maintenance. Naltrexone is allowed—about 18 percent of residents are or have been on it—and the clinic is seeking ways to increase the use of the XR-NTX. Staff are trained in the use of naloxone for rescue.
- There is a blackout period for the first 45 days the men are in treatment, and they are not allowed to go anywhere outside of the treatment facility during this time. Residential patients may stay for up to 2 years, and some become Helping Up Mission staff.
- In 2011, Mission staff reached out to Johns Hopkins because they wanted an evidence-based model for on-site SUD treatment and Hopkins had an existing non-pharmacologic model in place at its Bayview location. It is a reinforcement-based treatment model that is evidence-based and is a combination of CBT, motivational interviewing, and contingency management, with individualized goal setting and incentivized attendance.
- The Cornerstone clinic at Helping Up Mission opened in 2012 with 5 clients and now has about 60 clients, 4 counselors, a clinical supervisor, and a patient services coordinator,

providing group and individual therapy sessions. The clinic has been accredited by the Commission on Accreditation of Rehabilitation Facilities (CARF).

- The clinic treats mostly white (55 percent) and African American (39 percent) clients, 21–60 years old; 87 percent are single, separated, or divorced; and 22 percent have been incarcerated or detained within 30 days of intake.
- Drugs used before residents arrive for treatment include alcohol, heroin, cocaine, marijuana, and prescription pain relievers. The program is 100-percent Medicaid-funded (fee-for-service) and is financially viable. Mean duration of treatment is about 4 months.
- Strengths of the program are proximity, low relapse rate, financial viability, opportunities for clinical training, and a stable population for health services outcome data.
- Limitations: There is no women's programming, but the clinic is currently seeking funding to create a women's program arm. A challenge is integration of philosophy with partners. Also, there is no on-site dispensing of medication; it is currently handled through referrals, and so it is difficult to attribute treatment success to one source.
- Opportunities for improvement include collecting quality improvement data demonstrating health behavior outcomes (e.g., relapse rates and urinalysis rates), which the clinic began for the CARF accreditation process. Other opportunities include possibly providing on-site psychiatric care, developing a research infrastructure, and expanding the staff.
- Ongoing considerations include the reimbursement structure (working out so far, but rates may change), physical space constraints, accreditation demands, service coordination with other partners, and protection of client confidentiality while working with partners.
- In conclusion, academic and community partnerships are feasible; it is important to meet persons where they are geographically; the program has high attendance and low relapse rates; and there is growth potential in the clinical and research domains.

Collaborative Care for Patients with Substance Use Disorders in Outpatient Settings

Presenter: Colleen T. LaBelle, MSN, RN-BC, CARN, Nurse Manager, Boston Medical Center Office-Based Addiction Treatment; Director, Program Director, State Technical Assistance Treatment Expansion Office Based Opioid Treatment (STATE OBOT), Massachusetts Department Public Health; Executive Director, Massachusetts International Nurses Society on Addictions, Boston Medical Center
(Conflict of interest disclosure: None reported.)

Key points: A collaborative model of care, with a multidisciplinary team that uses nurse practitioners (NPs) and/or physician's assistants (PAs) in the delivery of care, permits efficient use of limited physician time to focus on patient management. It also allows patients with complex medical needs to be treated in medical settings without taxing all the providers. NPs and PAs are primary providers and prescribers of non-agonist medications, working in many community and criminal justice settings. The NP and PA workforce is growing and is helping to expand treatment; provide chronic disease management; provide services in rural and low-income settings; utilize the multidisciplinary team approach; place an emphasis on prevention, education, and costs; and facilitate access to care and to evidence-based care.

- The Boston Medical Center's program is a collaborative model of care, with a multidisciplinary team that uses registered nurses (RNs) as nurse care managers. The model allows for the efficient use of physician time to focus on patient management. It also allows

patients with complex medical needs to be treated in medical settings without taxing all the providers.

- There is open communication between the nurse care manager and other providers, including behavioral health improvement compliance. There is office-based opioid addiction treatment (OBOT) and daily management of complex psychosocial needs, such as housing, employment, and health insurance.
- These programs decrease costs but do not impact the quality of care people receive. The role of NPs in the primary care arena expands access to care, addresses the shortage of physicians, encourages team-based care, and improves access to care in communities.
- NPs' and PAs' role in the management of non-agonist medication includes facilitating access to treatment—being primary providers and prescribers—working in many community settings, including detox, mental health centers, minute clinics, community centers, addiction treatment centers, and criminal justice settings.
- The importance of NPs and PAs providing treatment with non-agonist medication includes expanding access to primary care providers treating addiction (especially given the shortage of physicians). It promotes team-based care; NPs and PAs teach patients about treatment; the treatment is sustainable and billable; costs are down; and the outcomes are equal to physicians' hospital readmissions.
- NPs are in the office 5 days a week, when the doctor may not be there. They help with a lot of the complexities of Vivitrol. NPs can get people involved in real time, and patients don't have to wait for their injections or go to another facility to get them.
- Having a multidisciplinary team with RNs working with prescribers decreases the burden of complex care management. This team can assist with follow-up assessments (urine screens, labs, challenge, relapse); allow for access to treatment providers (emergency issues, surgical procedures); support medication tracking, ordering, and delivery; assist with the transition from full to partial to antagonist; and enable contacting patients for missed appointments early on in treatment.
- The multidisciplinary team makes for a seamless transition for a variety of situations, including post-incarceration, probation, parole, discharge from inpatient, emergency encounters, detox admissions, residential settings, return to prior neighborhood, mental health concerns, and personal relapse concerns, i.e., stressful events and other issues.
- The NP and PA workforce is growing and is helping to expand treatment; provide chronic disease management; provide services in rural and low-income settings; utilize the multidisciplinary team approach; place an emphasis on prevention, education, and costs; and facilitate access to care and to evidence-based care. There is a larger percentage of NPs and PAs in community settings, and leveraging this workforce can greatly expand access to MAT.
- A barrier to expanding this type of care is health centers wanting to continue what they are used to, as opposed to learning about how to obtain the drug, store it, etc. Another challenge: MAT clinics are getting more referrals of acutely ill people. Alcohol patients stay on naltrexone treatment longer than opioid patients. Patients sometimes come in asking for one medication, and this can be a great tool to engage them into care. If the treatment isn't effective, you still have a patient who is now working with providers, building relationships, and may now be willing to try other treatment options. There is a need for training to provide practitioners with the skills to work in multidisciplinary teams and to communicate with and listen to each other.

Federal Bureau of Prisons – Medication-assisted Therapy

Presenter: Chris A. Bina, Rear Admiral, U.S. Public Health Service; U.S. Assistant Surgeon General; Senior Deputy Assistant Director, Health Service Division, Federal Bureau of Prisons (Conflict of interest disclosure: None reported.)

Key Points: The Federal Bureau of Prisons (BOP) has begun to offer MAT through a field trial. There have been zero opioid-related deaths in federal prisons since tracking started a few years ago, and the focus has been on people leaving prison and returning to society. Offenders are given two shots of naltrexone inside the prison and six outside, and a telehealth model is used after they leave the prison. The program is challenging once the offender leaves a BOP institution and requires a tremendous amount of time and communication for BOP staff. A model being considered is a pharmacy benefits management package that provides a released offender with a prescription benefit while at a halfway house or in home confinement.

- Correctional health is public health, and correctional medicine is a specialty of its own (Carmona, 2003). Of all the patients in correctional facilities, 95 percent will return to the communities from which they came.
- History of MAT in the Bureau of Prisons: A 2-year NIDA/Texas Christian University study that looked at the feasibility of providing MAT in a correctional environment led to a field trial with three institutions feeding into two halfway houses. There has been increasing interest in MAT in prisons.
- Because of the Presidential Executive Memorandum, federal prescriber training was provided for BOP physicians and dentists.
- The Federal Bureau of Prisons strategy considers the importance of good intake procedures and detox protocols; negative patient outcomes; security issues; community MAT trials and whether they translate to highly structured correctional environments; the risk of overdose and relapse being exponentially greater when individuals are released; and the groups found to have the largest potential for positive outcomes.
- Agonist therapy has a history of abuse within correctional systems.
- There have been zero opioid related deaths within the BOP since tracking started a few years ago. The focus is on people leaving the prison system and re-entering the community.
- Why naltrexone? As an antagonist, it has many advantages over agonist therapy within the correctional environment.
- Within the field trial, the offender is given two shots of naltrexone inside the prison and six outside. A telehealth model is used after they leave the prison.
- A model being considered is a pharmacy benefits management program so that a released offender will have a prescription benefit while at a halfway house or in home confinement. Dedicated BOP staff will be needed to coordinate this effort and communicate the numerous touch points involved with the delivery, administration, and follow-up of these patients once they leave the institution.
- The National Institute of Corrections, American Correctional Association, and U.S. Probation Office are all discussing the issue of MAT.
- It is not yet clear if six shots is the magic number. Internal social workers can help returning citizens connect with their communities. A big question is how MAT affects long-term recidivism—and how that is defined.

XR-Naltrexone: Implementation Models

Presenter: David Gastfriend, MD, DFASAM, Scientific Advisor for the Treatment Research Institute; Chief Architect, CONTINUUM: The ASAM Criteria Decision Engine
(Conflict of interest disclosure: Consultant: Alkermes, Indivior, Kaleo; advisory board or committee: Alkermes, Indivior, Kaleo; equity holdings: Alkermes.)

Key points: There are studies of a number of XR-NTX implementation models. A study in Pennsylvania showed that XR-NTX can be successfully administered to opioid-dependent patients after detox and before discharge from inpatient rehab. A Massachusetts study found that XR-NTX begun in opioid rehab can be continued in primary care. In another study, inmates in two Massachusetts counties who received XR-NTX before release showed strong adherence to the program and low recidivism rates when follow-up was done. The Missouri Departments of Behavioral Health and of Corrections together offered opioid-dependent probationers and parolees MAT with various medications and found that treatment with XR-NTX led to higher retention and abstinence rates than with all other medications. In a Florida program to increase providers' comfort with prescribing XR-NTX, a survey showed that providers need basic medical knowledge and help with protocols and patient selection, patient education, retention, psychosocial treatment planning, logistics, pharmacy procedures, regulations, reimbursement, documentation, and managing agency culture.

- There are quite a few implementation models across the country. Studies of some are described in this presentation.
- CRC Health Group, Inc. (CRC), the largest U.S. private provider of addiction treatment at the time of this study, naturalistically looked at three groups at three sites in Pennsylvania. One group of 168 patients received one XR-NTX injection while in rehab for opioid dependence; 430 were not injected, but wanted and were prescribed XR-NTX; and 7,089 were not offered and did not receive XR-NTX. Findings: Patients who got an XR-NTX injection were significantly more likely to complete treatment and had longer lengths of stay and greater entry into continuing care. Conclusion: XR-NTX can be successfully administered to opioid-dependent patients after detox and before discharge from inpatient rehab.
- In another study done in Fall River, Massachusetts, participants were given the first dose of XR-NTX in inpatient rehab and were sent to a primary care doctor for the second injection. Conclusion: XR-NTX begun in opioid rehab can be feasibly continued in primary care.
- Two counties in Massachusetts, Middlesex and Barnstable, started programs for released inmates, giving them an injection of XR-NTX 2–7 days pre-release. Findings: 50 percent of those released in Barnstable were still drug-free 2 years later, and their recidivism rate was 12 percent. In Middlesex, 78 percent of those released adhered to the program, the recidivism rate was 9 percent, and inmate self-referrals led to a 50 percent growth in the treatment group in 2 months.
- The Missouri Division of Behavioral Health facilitated MAT in state-funded SUD treatment providers for patients with both OUD and AUD. The Division and the Department of Corrections created a pool of funds for MAT for probationers and parolees, which funded medication and related clinical care for those not eligible for Medicaid. Over a 1-year period,

2,882 people were treated; 156 received XR-NTX, 45 received oral naltrexone, 168 received buprenorphine and naloxone, and 2,513 received no medication. Result: The retention and abstinence rates for opioid patients receiving XR-NTX were substantially higher than for those in the other groups.

- Florida's statewide Peer Mentoring Project used peer mentoring to get clinicians who were uncomfortable with prescribing XR-NTX more comfortable with it, seeking to meet the MAT needs of patients with SUD, of treatment programs, and of Florida justice system entities that relate to them. Programs and providers included courts, jails, treatment programs, state psychiatric hospitals, and prescribers. Survey conclusions: Most programs have limited experience with XR-NTX and need basic medical knowledge and help with protocols and patient selection, patient education, retention, and psychosocial treatment planning as well as logistics, pharmacy procedures, regulations, reimbursement, documentation, and managing agency culture. There is distrust between the courts and the treatment providers that makes communication between them difficult. More experience with XR-NTX is associated with higher perception of its effectiveness.
- The Ohio Drug Court system conducted a pilot program to provide MAT and ancillary services to offenders in drug court who volunteered because of dependency on opioids, alcohol, or both. Of 366 drug court participants from seven sites enrolled in the program, 5 percent were given Vivitrol, 14 percent were given other MAT, and 8 percent received no MAT. Pilot findings: At 6 months from drug court discharge, none of the participants on Vivitrol had used heroin in the past 30 days, 10 percent of those on other MATs had used it, and 4 percent of those who received no MAT had used it. Now there is ongoing evaluation of a 2-year program, pairing courts with treatment providers.
- In a multi-state survey by the Treatment Research Institute among 45 early-adopter criminal justice sites using XR-NTX, training was a big factor in sites' decision to use it. Survey results: More than 70 percent of the respondents said that XR-NTX was very effective for preventing relapse, 38 percent said it was very effective for preventing re-arrest, and 63 percent said it was very effective overall.

Key points in the discussion following the four presentations on provider considerations:

- Getting doctors to prescribe antagonists will not necessarily encourage them to prescribe agonists.
- The term "recovery" is used a lot, but it has been hard to find a good definition of it. The American Society of Addiction Medicine (ASAM) now offers a definition online. There is also a tool called the Recovery Index, with a checklist, that might be helpful.
- One model for peer mentoring: Local learning collaboratives are being established around the country, with lead organizations and monthly conference calls and knowledge sharing.
- A proactive outreach model (such as in Florida), using data from the treatment providers to determine who needs more mentoring, is a management strategy—an important component of a peer mentoring approach. Missouri uses a similar approach: State will not pay a provider unless all the treatments are provided.
- HIV and AIDS networks can be used as a model for spreading the word and implementing these treatment programs. HIV is still an issue.
- There are few women in MAT studies. The issue is whether we need gender-focused treatment programs or not.

Closing and Next Steps

Dr. Mitra Ahadpour thanked everyone on behalf of SAMHSA and NIDA. She stated that the meeting was very engaging and useful and that there was a lot of great information shared. Dr. Ahadpour said that next steps include the development of a summary report of the proceedings, which will go through clearance and will then be shared with the public. She closed by expressing her gratitude for everyone coming and sharing their research and work with the group.

APPENDIX A: MEETING PRESENTERS AND PARTICIPANTS

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APPENDIX B: MEETING AGENDA

Agenda

8:30–8:35 a.m. **Opening Remarks: Kimberly Johnson, PhD**

Welcome: Mitra Ahadpour, MD, DABAM

8:35–9:00 a.m. **Introductions: Joshua Lee, MD, MS (Chairperson)**

9:00–9:30 a.m. **Naltrexone: Overview and Opportunities for Psychosocial Treatments**

- Naltrexone pharmacology: Overview and research
  David Gastfriend, MD, DFASAM
- Examination and application of psychosocial treatments in conjunction with naltrexone
  Louis Baxter, Sr., MD, DFASAM, DABAM

9:30–11:15 a.m. **Clinical Considerations**

Discussion Topics **A Primer on Antagonist-based Treatment of Opioid Use Disorder in the Office Setting**

Joshua Lee, MD, MS; Adam Bisaga, MD, Richard Schottenfeld, MD

11:15–11:30 a.m. **Questions and Answers**

11:30–12:30 p.m. **Lunch**

12:30–1:15 p.m. **Clinical Considerations, continued**

Discussion Topics

- Improving inpatient detoxification and outpatient induction
  - Detoxification protocols compatible with naltrexone initiation (Hazelden)
    Pamela J. Shultz, MD, FASM

Preventing and reducing overdose including education for patients and clinicians
Joshua Lee, MD, MS

- Emerging therapies (e.g., lofexidine)
  Charles Gorodetzky, MD, PhD

1:15–1:45 p.m. **Questions and Answers**

1:45–3:00 p.m. **Patient Population Considerations**

Discussion Topics

- Patient choice and individualized treatment
  Robert Schwartz, MD
- Extended-release naltrexone for persons living with HIV with opioid and alcohol use disorders
  Sandra Springer, MD
- American Indians and Alaska Natives: Patient population considerations

Alec Thundercloud, MD

- Naltrexone in pregnancy
  Elisabeth Johnson, PhD, NP
- Special populations: Adolescents and young adults
  Marc Fishman, MD
- Individuals with co-occurring disorders: Naltrexone and comorbid conditions
  Paolo Mannelli, MD

3:00–3:15 p.m. **Questions and Answers**

3:15–3:30 p.m. **Break**

3:30–4:25 p.m. **Provider Considerations**

Discussion Topics

- Cornerstone at Helping Up Mission Clinic: Physicians in underserved areas
  Denis Antoine, MD
- Collaborative care for patients with substance use disorders in outpatients settings
  Colleen T. LaBelle, MSN, RN-BC, CARN
- Federal Bureau of Prisons – Medication-assisted therapy
  Rear Admiral Chris A. Bina, PharmD
- XR-Naltrexone: Implementation models
  David Gastfriend, MD, DFASAM

4:25–4:40 p.m. **Questions and Answers**

4:40–5:00 p.m. **Next Steps and Wrap-up**

APPENDIX C: REFERENCES

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