Background:
According to the Substance Abuse and Mental Health Services Administration’s (SAMHSA) 2016 National Survey on Drug Use and Health, an estimated 2.1 million Americans have opioid use disorder (OUD) due to either prescription opioids, heroin, or both. In 2014, 28,000 people died of an opioid overdose, which was a 400% increase from 1999. By 2016, according to the CDC, the annual number of opioid overdose deaths rose to exceed 42,000 more than the annual death rate from motor vehicle accidents, and the highest number recorded in a single year. The epidemic of opioid overdose deaths is even more pronounced in Indian Country, with rural areas hit hardest. Among American Indian and Alaska Native people in metropolitan and non-metropolitan areas, the rates of drug overdose deaths from 1999 to 2015 rose 261 and 519 percent respectively.

In August 2018, the NPTC undertook a comprehensive review of OUD and its treatment. As a result, the NPTC added (1.) buprenorphine-naloxone, (2.) buprenorphine (limited to management of OUD in pregnancy), and (3.) extended-release naltrexone to the IHS National Core Formulary.

Discussion:
Opioid use disorder is characterized by pervasive inappropriate and excessive use of opiates, drug-craving and drug-seeking behaviors, adverse social functioning, failure to meet core responsibilities, risk-taking behavior, drug tolerance, and withdrawal symptoms. Treatment objectives for individuals with OUD include harm-reduction strategies focused on management of overdose, medically supervised withdrawal (also known as detoxification) and medication-assisted therapy (MAT) for maintenance treatment, which commonly includes opioid substitution therapy. Several drug classes may be used in the management of OUD including the opioid receptor agonist methadone, the partial opioid receptor agonist buprenorphine, opioid receptor antagonists, naloxone and naltrexone, and the alpha-2 adrenergic agonists, clonidine and lofexidine.

Naloxone is an opioid antagonist indicated for partial or complete reversal of opioid depression. It has a rapid onset and is short-acting. As a single agent, it is used to treat acute opioid overdose. It is also used for diagnosis of suspected opioid overdose in emergency settings when the presentation is CNS-related and/or respiratory depression. Naloxone co-prescribing for certain patients on a prescription opioid is an essential component of harm reduction.

Medically-supervised opioid withdrawal involves medication administration to reduce the severity of withdrawal symptoms resulting from the discontinuation of opioids. The goal of supervised withdrawal is the safe transition to MAT of OUD. Short-term detoxification is aided by serial assessment of withdrawal symptoms using a well-validated observation instrument such as the Clinical Opioid Withdrawal Scale (COWS). It should be noted that detoxification alone does not promote sustained abstinence.

Medication-assisted therapy is an evidence-based management strategy for OUD with three components; maintenance pharmacotherapy, behavioral treatment, and patient monitoring. MAT is a proven strategy for reducing mortality from opioid overdose.

The first drug for MAT of opioid use disorder was methadone. Its primary use is for detoxification and maintenance treatment of opioid addiction. Its principle mechanism of action is binding of CNS opiate receptors where it alters perception of pain and induces CNS depression.

Another agent useful for maintenance treatment of opioid dependence is buprenorphine, a partial opioid agonist whose high-affinity for the mu opioid receptor causes it to act as an opioid receptor antagonist at higher doses. This high affinity results in an analgesic ceiling effect, reducing overdose risk and causing displacement of full agonist opioids, facilitating use in treatment of opioid dependence. Buprenorphine is available in a variety of formulations including a sublingual tablet, buccal film, transdermal patch, injection, and subcutaneous implant. Naloxone, which has limited oral bioavailability, may be combined
with buprenorphine in oral trans-mucosal formulations to reduce the potential for abuse. To further reduce
abuse potential and the risk for diversion, buprenorphine for OUD is intended to be part of a broader
treatment plan, including components of close treatment monitoring and limited at-home dosing.

Buprenorphine as monotherapy for OUD is recommended for pregnant patients, due to the risk of
neonatal withdrawal syndrome. Buprenorphine prescribing for the management of OUD was expanded
outside the confines of a federally recognized Opioid Treatment Program by the Drug Addiction and
Treatment Act of 2000. Qualified physicians may apply for a waiver to treat opioid-dependent patients
following completion of 8 hours of training and certification by the DEA. Notably the Comprehensive
Addiction and Recovery Act of 2016 expanded prescribing authority for buprenorphine to Nurse
Practitioners and Physician Assistants.

Naltrexone is a competitive antagonist of opioid receptors indicated for management of alcohol
dependence and opioid dependence. Unlike naloxone, naltrexone has a slow onset, which makes it
ineffective for reversal of overdose. Combined with the extended duration of action, this makes it
potentially more useful for the chronic management of OUD, where the extended-release formulation is
preferred. Naltrexone blocks the euphoric and sedative effects of opioids by competitive inhibition of
opioid receptors. It has been shown to decrease cravings as well as reactivity to drug-conditioned cues.
Naltrexone does not require specialized authorization or training to prescribe or dispense.

The alpha-2 adrenergic agonists, including clonidine and lofexidine, can be useful for the mitigation of
opioid withdrawal symptoms to facilitate abrupt opioid discontinuation. They are not for use in the long-
term management of OUD. Intended use includes correctional facilities or other environments that
prohibit controlled substances. Alpha-2 agonists produce autonomic symptom relief but do not address
craving and are therefore not preferred by most patients experiencing opioid withdrawal.

A variety of systematic reviews have assessed the efficacy of pharmacologic agents for the management
of OUD. In a 2009 Cochrane review, methadone appeared significantly more effective than non-
pharmacological approaches in retaining patients in treatment and in suppression of heroin use as
measured by self-report and urine/hair analysis (RR = 0.66, 95% CI: 0.56-0.78). A separate Cochrane
review in 2013 evaluated the effectiveness of tapered methadone compared with other detoxification
treatments and placebo in managing opioid withdrawal, on the completion of detoxification, and the
relapse rate. Comparing methadone with placebo, more severe withdrawal and more drop-outs were
found in the placebo group.

In 2016, the Cochrane group reviewed maintenance agonist pharmacotherapy, comparing full opioid
agonists, buprenorphine, and placebo for the treatment of opioid dependence. The reviewers found no
difference between methadone and buprenorphine in self-reported opioid use (RR 0.37, 95% CI: 0.08 to
1.63), opioid positive urine drug tests (RR 0.81, 95% CI: 0.56 to 1.18), retention in treatment (RR 0.69,
95% CI: 0.39 to 1.22), or adverse events (RR 1.10, 95% CI: 0.64 to 1.91). Compared to detoxification or
psychological treatment, maintenance buprenorphine was found superior in fewer opioid positive urine
tests (RR 0.63, 95% CI: 0.43 to 0.91), self-reported opioid use (RR 0.54, 95% CI: 0.31 to 0.93), retention
in treatment (RR 0.33, 95% CI: 0.23 to 0.47), and adverse events (RR 0.19, 95% CI: 0.06 to 0.57). In a
follow-up Cochrane review in 2017, no difference was found between buprenorphine and methadone in
terms of average treatment duration (mean difference: 1.30 days, 95% CI: 8.11-10.72) or treatment
completion rates (RR 1.04, 95% CI: 0.91-1.20).

In 2016, the Agency for Healthcare Research and Quality supported a systematic review to evaluate
models of care integrating medication assisted treatment into primary care settings for the management
of OUD. Multi-disciplinary stakeholders identified 4 key components of MAT in primary care which were;
1) pharmacotherapy with buprenorphine or naltrexone, 2) provider and community educational
interventions, 3) community-based advertising campaigns, and 4) stakeholder conferences.

In 2017, a systematic review published in PlosOne also sought to analyze current evidence-based
primary care MAT interventions for OUD. Successful studies were defined by 60% retention at 3 months
and nearly all shared several common characteristics including a coordinated care model with a
multidisciplinary team, pharmacotherapy with buprenorphine, a behavioral health component, a nurse
care coordinator, and treatment monitoring using urine screens.
While methadone, buprenorphine, and naltrexone have all been found to be effective compared to placebo, a number of trials have evaluated the comparative effectiveness of these medications. A 2014 Cochrane review evaluated the effectiveness of buprenorphine compared to methadone.\textsuperscript{10} For retention in treatment, buprenorphine was found to be less effective than methadone (RR 0.83; 95% CI: 0.72-0.95) while, for suppression of opioid use, no difference was found either by urinalysis (SMD -0.11, 95% CI: -0.23 to 0.02) or patient self-report (SMD -0.11, 95% CI: -0.28 to 0.07).

A multi-center, outpatient, open-label randomized clinical trial published in 2017 compared extended-release naltrexone with oral buprenorphine-naloxone among newly detoxified opioid-dependent adults over 12 weeks.\textsuperscript{11} Compared with buprenorphine-naloxone, extended-release naltrexone was non-inferior with regard to retention in treatment (difference, −0.1, 95% CI: −0.2 to 0.1), negative urine drug tests (difference, 0.1, 95% CI: −0.04 to 0.2), heroin use (difference, −3.2, 95% CI: −4.9 to −1.5), and use of other illicit opioids (difference, −2.7, 95% CI: −4.6 to −0.9). The authors concluded that maintaining short-term abstinence from illicit opioids and other substances with extended-release naltrexone was as effective and safe as buprenorphine-naloxone, and that extended-release naltrexone should be an available treatment option for opioid dependent individuals. A 2018 study found that extended-release naltrexone had a substantial induction hurdle in that fewer participants successfully initiated it than buprenorphine-naloxone.\textsuperscript{12}

Earlier this year, SAMHSA published a treatment improvement protocol regarding medications for OUD.\textsuperscript{13} This guideline focuses on three medications; methadone, buprenorphine, and extended-release naltrexone, favoring an individualized approach to selection of an agent. While duration of therapy is not defined, the high rate of relapse after discontinuation of medication for treatment is noted and extended treatment is advocated. The guideline advises against using medically supervised withdrawal alone, due to the high rate of relapse. When used as part of a broader treatment plan, methadone and buprenorphine are recommended along with medications for symptom control.

National data on OUD highlight a significant treatment gap between the number of those needing treatment and programs with the capacity to provide that treatment. According to SAMHSA, as of 2012, 80% of national opioid treatment programs were operating at over 80% capacity and the number of people unable to access treatment approached 1 million.\textsuperscript{14} Meanwhile, data from SAMHSA’s treatment episode data set in 2015 further revealed that among patients enrolled in treatment in a specialty facility, only 37% with heroin use disorder and 31% with non-heroin opioid use disorder were receiving MAT.

In response to recent increases in opioid-related morbidity and mortality, the U.S. Department of Health and Human Services made addressing the opioid abuse problem a high priority and is focused on implementing evidence-based approaches. Three priority areas have been identified, including changing opioid prescribing practices to reduce OUDs and overdose, expanded use of naloxone, and expanded use of medication-assisted treatment.

**Findings:**

Opioid use disorder is highly prevalent, with rising incidence of overdose deaths, especially among American Indians and Alaska Natives. As a harm reduction strategy, community-based naloxone use effectively prevents opioid overdose deaths. MAT is proven effective in retaining patients in treatment, reducing illicit opioid use, and preventing opioid-related deaths. MAT strategies consisting of an opioid agonist are most effective.

Methadone and buprenorphine have similar efficacy, but buprenorphine is safer and more convenient. Two options exist for office-based long-term treatment of OUD: buprenorphine-naloxone and naltrexone. Office-based treatment with buprenorphine-naloxone, using a coordinated care model, enhances access to MAT. Extended-release naltrexone, when successfully initiated, may be a reasonable alternative to buprenorphine-naloxone. Alpha-2 agonists have a limited role in managing withdrawal in certain settings (criminal justice system).

*If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.*
References: