Michael R. Pence, Governor
State of Indiana

Indiana Family and Social Services Administration
402 W. WASHINGTON STREET, P.O. BOX 7083
INDIANAPOLIS, IN 46207-7083

Best Practice Guidelines for the Treatment of Opioid Use Disorders
Division of Mental Health and Addiction

December 30, 2016

These best practice guidelines were developed in response to Indiana Senate Enrolled Act (SEA) 297 & SEA 214 (2016). The intent of the guidelines is to provide a standard of care for the treatment of opioid use disorders (OUDs) in the State of Indiana and will be sent to the Indiana Professional Licensing Agency, the Office of Medicaid Policy and Planning, and the managed care organizations contracted with the Office for implementation. Practice standards were determined through a review of existing guidelines and research base. The Indiana guidelines are intended to quickly assist providers in locating up to date, accurate and useful information. Leslie Hulvershorn, MD, Medical Director at the Indiana Division of Mental Health and Addiction (DMHA), was the primary author. Information was then reviewed within DMHA and was circulated for review to stakeholders, such as Mental Health America of Indiana, Addiction Psychiatry faculty and fellows from the Indiana University School of Medicine, and CleanSlate Centers. This guide applies to inpatient and office-based opioid treatment (OBOT) providers and Opioid Treatment Providers (OTPs; i.e., "methadone clinics") in their use of buprenorphine and naltrexone. Sections within quoted material marked by "[*text in italics*]" should be interpreted as additional text provided by the authors of the Indiana guidelines, not a part of the originally published material (e.g., American Society of Addiction Medicine guidelines). These guidelines are not intended to be a substitute for formal medical training in the treatment of substance use disorders. The definition of 'physician' in these guidelines includes all DATA-waved clinicians who prescribe buprenorphine for addiction treatment legally under their license in Indiana.

Abbreviations
American Psychiatric Association = APA American Society of Addiction Medicine = ASAM
Medication assisted treatment= MAT
Opioid use disorders= OUDs
Office-based opioid treatment = OBOT (e.g., DATA waived physicians)
Opioid treatment programs=OTPs (Require particular license from DEA; Offer daily supervised dosing of methadone, and other medications)

Table of Contents

Guideline Summary:
Comprehensive treatment, including medication assisted treatment (MAT), is an effective response to opioid use disorder (OUD). The use of medications, in combination with behavioral therapies, provides a whole-patient approach to the treatment of substance use disorders. Individuals receiving MAT often demonstrate dramatic improvement in addiction-related behaviors and psychosocial functioning.

The opioid use disorder treatment protocol shall have the goal of opioid abstinence when appropriate or, if not possible, the minimal clinically necessary dose of medication. Treatment providers shall provide themselves, or through referral, comprehensive treatment options, including:

1. Opioid maintenance;
2. Opioid detox;
3. Overdose reversal;
4. Relapse prevention;
5. Long acting, nonaddictive medication assisted treatment medications.

Treatment for opioid use disorders shall be comprehensive and include:

1. Initial and periodic behavioral health assessments for each patient;
2. Informed consent from a concerning all available opioid treatment options, including each option's potential benefits and risks, before prescribing medication;
3. Appropriate use of providing overdose reversal medication, relapse prevention, counseling and ancillary services;
4. Transitioning off agonist and partial agonist therapies, when appropriate, with the goal of opioid abstinence.

Section 1. Assessment and Diagnosis of opioid use disorders for Office-based opioid treatment (OBOT) providers

Introduction:
In order to appropriately assess for opioid use disorders, as well as co-occurring mental health, other substance use disorders and physical health, best practices have been reviewed. Essential information about these best practices is as follows:

For any provider treating opioid use disorders (OUDs), the following practices are recommended for assessment and diagnosis.

Assessment & Diagnosis Recommendations (excerpted from American Society of Addiction Medicine (ASAM) Guidelines [1]):
"(1) First clinical priority should be given to identifying and making appropriate referral for any urgent or emergent medical or psychiatric problem(s), including drug related impairment or overdose.
(2) Completion of the patient's medical history should include screening for concomitant medical conditions including infectious diseases (hepatitis, HIV, and TB), acute trauma, and pregnancy. [*If the provider does not provide this type of medical screening, the patient should be referred to a provider who does and any findings (if not readily identifiable in the medical record) should be reported to the provider treating the OUDs.*]

(3) A physical examination should be completed as a component of the comprehensive assessment process. The prescriber (the clinician authorizing the use of a medication for the treatment of opioid use disorder) may conduct this physical examination him/herself, or, in accordance with the ASAM Standards, [*refer to another provider to*] ensure that a current physical examination is contained within the patient medical record before a patient is started on a new medication for the treatment of his/her addiction.

(4) Initial laboratory testing should include a complete blood count, liver function tests, and tests for hepatitis C and HIV. Testing for TB and sexually transmitted infections should also be considered. Hepatitis B vaccination should be offered, if appropriate.

(5) The assessment of women presents special considerations regarding their reproductive health. Women of childbearing age should be tested for pregnancy, and all women of childbearing potential and age should be queried regarding methods of contraception, given the increase in fertility that results from effective opioid use disorder treatment.

(6) Patients being evaluated for addiction involving opioid use, and/or for possible medication use in the treatment of opioid use disorder, should undergo (or have completed) an assessment of mental health status and possible psychiatric disorders (as outlined in the ASAM Standards). [*Any psychiatric disorders that are identified warrant treatment, either by referral or treatment directly by the OBOT provider. Periodic mental health screens (and subsequent treatment) should be completed by the OBOT provider every 3 months, or with the emergence of psychiatric symptoms (e.g., depression, psychosis), whichever occurs first.*]

(7) Opioid use is often co-occurring with other substance related disorders. An evaluation of past and current substance use and a determination of the totality of substances that surround the addiction should be conducted.

(8) The use of marijuana, stimulants, or other addictive drugs should not be a reason to suspend opioid use disorder treatment. However, evidence demonstrates that patients who are actively using substances during opioid use disorder treatment have a poorer prognosis. [*The use of benzodiazepines and other sedative hypnotics is a reason to suspend agonist treatment because of safety concerns related to respiratory depression. A thirty day benzodiazepine taper should be initiated at the onset of treatment or whenever the benzodiazepine use is discovered. On occasion, if ongoing withdrawal is clearly present and documented, a ninety day benzodiazepine taper may be warranted.*]

(9) A tobacco use query and counseling on cessation of tobacco products and electronic nicotine delivery devices should be completed routinely for all patients, including those who present for evaluation and treatment of opioid use disorder.

(10) An assessment of social and environmental factors should be conducted… Addiction should be considered a bio-psycho-social-spiritual illness, for which the use of medication(s) is but only one component of overall treatment."

Diagnostic Recommendations (excerpted from ASAM Guidelines [1]):

"(1) Other clinicians may diagnose opioid use disorder, but confirmation of the diagnosis by the provider with prescribing authority and who recommends medication use must be obtained before pharmacotherapy for opioid use disorder commences.

(2) Opioid use disorder is primarily diagnosed on the basis of the history provided by the patient and a comprehensive assessment that includes a physical examination.

(3) Validated clinical scales that measure withdrawal symptoms, for example, the Objective Opiate Withdrawal Scale (OOWS), Subjective Opiate Withdrawal Scale (SOWS), and the Clinical Opiate Withdrawal Scale (COWS), may be used to assist in the evaluation of patients with opioid use disorder.

(4) Urine drug testing during the comprehensive assessment process, and frequently during treatment, is recommended. The frequency of drug testing is determined by a number of factors, including the stability of the patient, the type of treatment, and the treatment setting."

Section 2. Appropriate use of medications for the treatment of Opioid Use Disorders by OBOT Providers

Introduction: Medications with a substantial evidence base supporting their efficacy in various stages of the treatment of opioid use disorders are reviewed in this section.
Specifically, evidence supporting detoxification, maintenance treatment, dosing recommendations and overdose reversal are reviewed. In addition, practices lacking an evidence base are also covered here.

(i) Opioid maintenance treatment options

Buprenorphine (excerpted from ASAM Guidelines [1]): "Treatment with buprenorphine for opioid addiction consists of three phases: (1) induction, (2) stabilization, and (3) maintenance. Induction is the first stage of buprenorphine treatment and involves helping patients begin the process of switching from the opioid of abuse to buprenorphine. The goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment (and for stabilization and maintenance) for most patients. The consensus panel further recommends that initial induction doses be administered as observed treatment; further doses may be provided via prescription thereafter... Pregnant women who are deemed to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy. The stabilization phase has begun when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and [*cravings have been significantly reduced*]. Dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance. The longest period that a patient is on buprenorphine is the maintenance phase. This period may be indefinite. During the maintenance phase, attention must be focused on the psychosocial and family issues that have been identified during the course of treatment as contributing to a patient's addiction[, *rather than on buprenorphine dose escalation.*]"

Minimum clinically necessary dosing (excerpted from ASAM Guidelines [1]): "(1) Opioid-dependent patients should wait until they are experiencing mild to moderate opioid withdrawal before taking the first dose of buprenorphine to reduce the risk of precipitated withdrawal. Generally, buprenorphine initiation should occur at least 6–12 hours after the last use of heroin or other short-acting opioids, or 24–72 hours [or more for individuals taking high doses of opioids] after their last use of long-acting opioids such as methadone.

(2) Induction of buprenorphine should start with a dose of 2–4 mg, [*with 8mg inductions being appropriate for a greater degree of physiologic dependence*]. Dosages [*are often*] increased in increments of 2–4mg.

(3) Clinicians should observe patients in their offices during induction.

(4) Buprenorphine doses after induction and titration should be, on average, at least 8mg per day. However, if patients are continuing to use opioids, consideration should be given to increasing the dose by 4–8mg (daily doses of 12–16mg). [*While the US FDA approves dosing to*

a limit of 24mg per day, there is little evidence for clinical benefit beyond 16mg. Dosing beyond 24 mg is not recommended.] In addition, the use of higher doses may increase the risk of diversion.

(5) Psychosocial treatment should be implemented in conjunction with the use of buprenorphine in the treatment of opioid use disorder. [*Buprenorphine prescribers should be in regular contact with the psychosocial treatment team in order to be aware clinical progress. Preferably, the psychosocial and prescribing providers are co-located and on the same treatment team.]*

(6) Clinicians should take steps to reduce the chance of buprenorphine diversion. Recommended strategies include frequent office visits (weekly in early treatment), drug testing, including testing for buprenorphine and [*metabolites (e.g., norbuprenorphine)*], and recall visits for pill counts. [*In the case of diversion, the opioid treatment provider must determine that the benefit to the patient in receiving the medication outweighs the potential risk of diversion resulting from the take home medication.*]

(7) Patients should be tested frequently for buprenorphine, other substances, and prescription medications. Accessing Prescription Drug Monitoring Program (PDMP) data *[(INSPECT) is] useful for monitoring.*]See Section V.2. below. If a patient tests positive for a controlled substance other than the buprenorphine prescribed, the clinician shall review the treatment plan and consider changes with the goal of opioid abstinence.

(8) Patients should be seen frequently at the beginning of their treatment. Weekly visits (at least) are recommended until patients are determined to be stable. There is no recommended time limit for treatment. [*Provider must determine and document that the benefit of the receiving a supply of medication to treat an opioid use disorder would outweigh the potential risk of diversion.]*

(9) Buprenorphine taper and discontinuation is [*generally*] a slow process and close monitoring is recommended… Patients should be encouraged to remain in treatment for ongoing monitoring past the point of discontinuation.

(10) When considering a switch from buprenorphine to naltrexone, 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone.

(11) When considering a switch from buprenorphine to methadone, there is no required time delay because the addition of a full mu-opioid agonist to a partial agonist does not typically result in any type of adverse reaction.

(12) Patients who discontinue agonist therapy and resume opioid use should be made aware of the risks associated with an opioid overdose, and especially the increased risk of death."

(ii) Detoxification

A. Buprenorphine detoxification (excerpted from ASAM Guidelines [1]): "Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone.... The goal of using

buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms. Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase. The consensus panel recommends that patients dependent on short acting opioids (e.g., hydromorphone, oxycodone, heroin) who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine/naloxone tablets. The use of buprenorphine (either as buprenorphine monotherapy or buprenorphine/naloxone combination treatment) to taper off long acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients' OTPs."

B. Clonidine detoxification (excerpted from the APA guidelines [2]): "Clonidine is a [non-addictive] centrally acting α2-adrenergic antihypertensive medication that effectively decreases the noradrenergic hyperactivity associated with opioid withdrawal. Clonidine is not approved for opioid withdrawal in the United States but has been extensively studied and used for this indication elsewhere. Clonidine reduces withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating but, unlike methadone, does little to reduce other symptoms such as muscle aches, insomnia, distress, and drug craving [3, 4]. As a non-opioid medication, clonidine has some advantages over methadone for withdrawal. For example, clonidine does not produce opioid-like tolerance or dependence or the post-methadone rebound in withdrawal symptoms [5]. In addition, patients completing a course of clonidine-assisted withdrawal can immediately be given an opioid antagonist (e.g., naltrexone) if indicated. The disadvantages of clonidine include its aforementioned inability to improve certain opioid withdrawal symptoms, associated hypotension that can be profound despite the use of low doses of this medication, and its possible sedative effects. Contraindications to the use of clonidine include acute or chronic cardiac disorders, renal or metabolic disease, and moderate to severe hypotension [6]. On the first day of clonidine-aided detoxification, a clonidine dose of 0.1 mg three times daily (totaling 0.3 mg per 24 hours) is usually sufficient to suppress signs of opioid withdrawal; inpatients can generally receive higher doses to block withdrawal symptoms because of the availability of medical staff to monitor the patient for hypotension and sedation. The dose is adjusted until withdrawal symptoms are reduced. If the patient's blood pressure falls below 90/60 mm Hg, the next dose should be withheld, after which tapering can be resumed while the patient is monitored for signs of withdrawal. In the case of short-acting opioids such as heroin, clonidine-aided withdrawal usually takes 4–6 days. Other medications may be used along with clonidine to treat withdrawal symptoms. In general, clonidine-assisted detoxification is easier to carry out and monitor in inpatient settings. Clonidine-induced sedation is also less of a problem for inpatients."

C. Clonidine-Naltrexone (Excerpted from APA [2]): "The combined use of clonidine and naltrexone for rapidly withdrawing patients from an opioid has been demonstrated to be safe and effective. Essentially, naltrexone-precipitated withdrawal is avoided by pretreating the patient with clonidine. This technique is most useful for opioid dependent patients who are in transition to narcotic antagonist treatment [*e.g., naltrexone*]. The limitations of this method include the need to monitor patients for 8 hours on the first day because of the potential severity of naltrexone-induced withdrawal and the need for careful blood pressure monitoring during the entire detoxification procedure."

D. Supplementary Medications (Excerpted from APA [2]): "Some clinicians and treatment programs have used medications targeting the symptoms of opioid withdrawal as the primary means for treating this condition. For example,…, antiemetics are prescribed to treat nausea and vomiting, NSAIDs are provided for muscle cramps, and antispasmodics [(e.g., dicyclomine)] are used to treat gastrointestinal cramping. There are limited controlled data about the use of such medications for the treatment of opioid withdrawal [8]…Diphenhydramine, hydroxyzine, and sedating antidepressants (e.g., doxepin, amitriptyline, trazodone) have been used for [*insomnia and anxiety.*] It should be noted that these medications have also been abused, although much less often than benzodiazepines [9]. Other medications such as NSAIDs and antispasmodics may be safely provided but appear to be less effective than mu agonist opioids for symptom relief."

(iii) Overdose Reversal (Excerpted from APA Guidelines [2]):
"The syndrome of acute opioid overdose is recognizable by respiratory depression, extreme miosis, and stupor or coma [10]. Pulmonary edema may also be observed. Naloxone is a competitive antagonist at all three types of opiate receptors (mu, kappa, and sigma) and has no intrinsic agonist activity [11]. It is clinically indicated to rapidly reverse a known or suspected opioid overdose [10, 12]…Because naloxone is rapidly absorbed by the brain and then quickly redistributed and eliminated from the body, its activity in the brain is short-lived [10, 13]. Thus, further monitoring and infusion of additional naloxone are needed to continue antagonizing the effects of severe opioid overdose, particularly if longer-acting opioids have been ingested [12, 14]. Monitoring for opioid withdrawal symptoms is also indicated because patients may experience significant distress that can last for several hours after reversal of an opioid overdose with an antagonist [9]." [*Currently, in the State of Indiana, naloxone is available without a prescription from individual prescribers, as pharmacies have a written order to prescribe from the State Health Commissioner. At the time of assessment, OBOT providers should provide education about naloxone's role in overdose reversal to all patients in treatment for OUDs, as well as any involved family, caregivers or friends.*

OBOT providers should recommend that patients in treatment obtain a supply of naloxone to use in case of an overdose, but provide education that not all overdoses can be rescued.]

(iv) Relapse prevention:
Relapse prevention is the use of pharmacologic and psychotherapeutic techniques that have been shown to decrease the risk of relapse in individuals in treatment for substance use disorders. See section 4 for psychotherapeutic techniques. FDA approved pharmacological treatments shown to reduce relapse in persons with OUDs include naltrexone, buprenorphine containing products and methadone.
Naltrexone (ASAM guidelines [1]):
"(1) Naltrexone is a recommended treatment for preventing relapse in opioid use disorder [*and is generally well tolerated*]. Oral formula naltrexone may be considered for patients in whom adherence can be supervised or enforced [*e.g., individuals who are incarcerated, adolescents supervised by parents, inpatients*]. Extended-release injectable naltrexone [*Vivitrol TM] may be*

more suitable for patients who have issues with adherence, [particularly individuals living in the community, receiving outpatient treatment.]
(2) [*Oral naltrexone should usually be taken daily in 50-mg doses.*]

(3) Extended-release injectable naltrexone [*Vivitrol TM*] should be administered every 4 weeks by deep IM injection in the gluteal muscle at a set dosage of 380 mg per injection.

(4) Psychosocial treatment, [*in conjunction with treatment with naltrexone, is required.*] The efficacy of naltrexone use in conjunction with psychosocial treatment has been established, whereas the efficacy of extended release injectable naltrexone without psychosocial treatment ''has not'' been established.

(5) There is no recommended length of treatment with oral naltrexone or extended-release injectable naltrexone. Duration depends on clinical judgment and the patient's individual circumstances. Because there is no physical dependence associated with naltrexone, it can be stopped abruptly without withdrawal symptoms.

(6) Switching from naltrexone to methadone or buprenorphine should be planned, considered, and monitored. Switching from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than switching from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment and thus no possibility of precipitated withdrawal. Patients being switched from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine used should be low. Patients should not be switched until a significant amount of the naltrexone is no longer in their system, about 1 day for oral naltrexone or 30 days for extended-release injectable naltrexone.

(7) Patients who discontinue antagonist therapy and resume opioid use should be made aware of the increased risks associated with an opioid overdose, and especially the increased risk of death.

(8) Naltrexone should be used with ''caution'' under the following conditions:
(a) All patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Hepatic injury is a concern if very high doses are used, for example, 200–300 mg per day. Use of naltrexone should be discontinued in the event of symptoms and/or signs of acute hepatitis. Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone exposure during the clinical development program and in the post marketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and post marketing period.

(b) Patients with [*clinically significant*] liver impairment should complete liver enzyme tests before and during treatment with naltrexone to check for additional liver impairment.

(c) Patients who experience injection site reactions should be monitored for pain, redness, or swelling. Incorrect administration may increase the risk of injection site reactions. Reactions

have occurred with extended-release injectable naltrexone. To reduce injection site reactions in obese patients, a longer needle size may be used.

(d) [*Patients with co-occurring psychiatric disorders should be monitored for [psychiatric] adverse events. Suicidal thoughts, attempted suicide, and depression have been reported [with naltrexone*]].

(9) Significant ‘‘medication interactions’’ with naltrexone are as follows:
(a) Naltrexone should not be used with methylnaltrexone or naloxegol.
(b) Naltrexone blocks the effects of opioid analgesics because it is an opioid antagonist.
(c) Glyburide may increase serum concentration of naltrexone. Monitor for increased toxicity effects of naltrexone.”

Section 3. Switching between medications that treat OUDs

Introduction: In order to assist providers with the process of switching between medications, detailed, current evidence is provided. Switching may be needed for the following reasons, including but not limited to: patient preference, side effects, difficulty accessing a particular medication, etc.

(Excerpted from ASAM guidelines [1]):
"(I) Switching from methadone to other opioid treatment medications may be appropriate in the following cases:
(1) Patient experiences intolerable methadone side effects.
(2) Patient has not experienced a successful course of treatment on methadone.
(3) Patient wants to change and is a candidate for the alternative treatment. Transfer of medications should be planned, considered, and monitored. Particular care should be taken in reducing methadone dosing before transfer to avoid precipitating a relapse. If the patient becomes unstable and appears at risk for relapse during the transfer of medications, reinstating methadone may be the best option.

(II) Switching from methadone to buprenorphine:

[*This medication switch should be referred or closely supervised by an experienced addictionologist.*] Patients on low doses of methadone (30–40mg per day or less) generally tolerate the transition to buprenorphine with minimal discomfort; whereas patients on higher doses of methadone may find that switching causes significant discomfort. Patients should be closely monitored during such a switch because there is a risk that stable methadone patients may become unstable when changing to buprenorphine...

Patients should be experiencing mild to moderate opioid withdrawal before the switch. This would typically occur at least 24 hours after the last dose of methadone, and indicates that sufficient time has elapsed for there to be minimal risk that the first dose of buprenorphine will precipitate significant withdrawal.
Moderate withdrawal would equate to a score greater than 12 on the COWS. An initial dose of 2–[*8*] mg of buprenorphine should be given and the patient should be observed for 1 hour. If withdrawal symptoms improve, the patient can be dispensed two additional 2–4-mg doses to be taken as needed.

(III) Switching from Methadone to Naltrexone

[*This medication switch should be referred or closely supervised by an experienced addictionologist. This process often takes place in inpatient settings.*] Patients switching from methadone to oral naltrexone or extended- release injectable naltrexone need to be completely withdrawn from methadone and other opioids before they can receive naltrexone. This may take up to 14 days, but can typically be achieved in 7 days. A naloxone challenge (administration of 0.4–0.8 mg naloxone and observation for precipitated withdrawal) may be useful before

initiating treatment with naltrexone to document the absence of physiological dependence and to minimize the risk for precipitated withdrawal.

(IV) Switching from Buprenorphine to Naltrexone

Buprenorphine has a long half-life; 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone to ensure that the patient is not physically dependent on opioids before starting naltrexone. It may be useful to conduct a naloxone challenge before starting naltrexone to demonstrate an absence of physical dependence. Recently, investigators have begun to evaluate newer methods of rapidly transitioning patients from buprenorphine to naltrexone using repeated dosing over several days with very low doses of naltrexone along with ancillary medications. Although the results are promising, it is too early to recommend these techniques for general practice, and the doses of naltrexone used may not be readily available to most clinicians. [*However, for physicians with addiction expertise, the American Academy of Addiction Psychiatry in partnership with the American Psychiatric Association, the American Society of Addiction Medicine, and the American Osteopathic Academy of Addiction Medicine provides the Columbia Rapid Naltrexone Induction Protocol at: http://pcssmat.org/wp-content/uploads/2015/02/PCSSMAT-Implementing- Antagonist-with-Case.Bisaga.CME_.pdf*]

(V) Switching to Methadone

Transitioning from buprenorphine to methadone is less problematic because the addition of a full mu-opioid agonist to a partial agonist does not typically result in any type of adverse reaction. There is no time delay required in transitioning a patient from buprenorphine to treatment with methadone."

Section 4. Counseling and Ancillary services for OBOT providers

Introduction: The combination of behavioral interventions and medications to treat substance use disorder is commonly referred to as MAT. While prescribing health care professionals can provide some or all of these interventions, some patients will require additional professionals to care for their medical, psychiatric, and addictive conditions. Best practice requires ensuring evidence-based interventions can be accessed as available, treatment should be individualized to the needs of the specific patient.

Excerpted from APA Guidelines [2]:
"When considering psychosocial treatments for treating opioid-related disorders, it is essential to note that all clinical trials of psychosocial interventions for opioid abusers have taken place in programs that also provide either opioid agonist maintenance (e.g., methadone) or treatment with opioid antagonists. Although some follow-up studies of naturalistic treatment have found equivalent efficacy for methadone maintenance and outpatient drug-free programs for heroin users [10, 15-18], early attempts at providing psychotherapy alone yielded unacceptably high attrition rates [19]."

Evidence based treatments which should be used to supplement medication assisted treatment for OUDs (excerpted from APA guidelines [2]):

"1. Cognitive-behavioral therapies
In individuals who are receiving methadone maintenance, CBT is efficacious in reducing illicit substance use and achieving a wide range of other treatment goals. The benefits of CBT in combination with drug counseling are equivalent to those of drug counseling alone or drug counseling plus supportive-expressive psychotherapy in patients with low levels of psychiatric symptoms; however, in the presence of higher degrees of depression or other psychiatric symptoms, supportive-expressive therapy or CBT has been shown to be much more effective than drug counseling alone [19-24]. CBT may also help reduce other target symptoms or behaviors (e.g., HIV risk behaviors) in opioid-using individuals [25]. Group based relapse prevention therapy, when combined with self-help group participation, may also help recently detoxified patients reduce opioid use and criminal activities and decrease unemployment rates [26].

2. Behavioral therapies

Contingency management approaches are beneficial in reducing the use of illicit substances in opioid-dependent individuals who are maintained on methadone [27- 29]. Although other reinforcers or rewards (e.g., vouchers for movie tickets or sporting goods) may be provided to patients who demonstrate specified target behaviors (e.g., providing drug-free urine specimens, accomplishing specific treatment goals, attending treatment sessions), methadone take-home privileges are a commonly offered and effective incentive that is made contingent on reduced drug use [30-33]. Furthermore, contingency management, either alone or in conjunction with family therapies, can also be used to enhance adherence with unpopular treatments such as naltrexone and has been shown to result in diminutions in drug use among recently detoxified opioid-dependent individuals [34-40].

3. Psychodynamic and interpersonal therapies

The utility of adding a psychodynamic therapy to a program of methadone maintenance has been investigated. The provision of supportive-expressive therapy, a specific approach to such treatment, may be particularly helpful for patients with high levels of other psychiatric symptoms [20, 23]. However, in terms of individual IPT, the potential benefits of treatment are unclear, as it is very difficult to engage opioid-dependent patients in such approaches. Psychodynamically oriented group therapy, modified for substance-dependent patients, appears to be effective in promoting abstinence when combined with behavioral monitoring and individual supportive psychotherapy [41].

4. Family therapies

Family therapy has been demonstrated to enhance treatment adherence and facilitate implementation and monitoring of contingency contracts with opioid- dependent patients [42, 43]. [*Family therapies are particularly beneficial for adolescents with OUDs*].

5. Self-help groups and 12-step-oriented treatments

Self-help groups, such as Narcotics Anonymous, are beneficial for some individuals in providing peer support for continued participation in treatment, avoiding substance-using peers and high-risk environments, confronting denial, and intervening early in patterns of thinking and behavior that often lead to relapse.

Because of the emphasis on abstinence in the 12-step treatment philosophy, patients maintained on methadone or other opioid agonists may encounter disapproval for this type of pharmacotherapy at Narcotics Anonymous meetings."

Section 5. Transitioning off agonist and partial agonist therapies, with the goal, when appropriate of opioid abstinence

Introduction: For many individuals, agonist treatments may be necessary until they have reached a point in their treatment where taper and discontinuation can be considered with their treatment providers.

Excerpted from ASAM guidelines [1]: "There is no recommended time limit for treatment with buprenorphine. Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended…Patients and clinicians should not take the decision to terminate treatment with buprenorphine lightly. Factors associated with successful termination of treatment with buprenorphine are not well described, but may include the following:

(1) Employment, engagement in mutual help programs, or involvement in other meaningful activities.
(2) Sustained abstinence from opioid and other drugs during treatment.
(3) Positive changes in the psychosocial environment.
(4) Evidence of additional psychosocial supports.
(5) Persistent engagement in treatment for ongoing monitoring past the point of medication discontinuation.

Patients who relapse after treatment has been terminated should be returned to treatment with buprenorphine."

Section 6. Training and experience requirements for providers who treat and manage individuals with OUDs

(1) Minimal Prescriber Requirements for Buprenorphine Prescribing

Excerpted from ASAM Guidelines [1]: "To practice office-based treatment of opioid addiction under the auspices of DATA 2000, physicians must first obtain a waiver from the special registration requirements established in the Narcotic Addict Treatment Act of 1974 and its enabling regulations. To obtain a DATA 2000 waiver, a physician must submit notification to SAMHSA of his or her intent to begin dispensing and/or prescribing this treatment. The Notification of Intent form must contain information on the physician's qualifying credentials and must contain additional certifications, including that the physician (or the physician's group practice) will not treat more than 30 patients for addiction at any one time.
Notification of Intent forms can be filled out and submitted online at the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov.

Physicians who meet the qualifications defined in DATA 2000 are issued a waiver by SAMHSA and a special identification number by DEA. To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications as defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to the necessary, concurrent psychosocial services. The consensus panel recommends that all physicians who plan to practice opioid addiction treatment with buprenorphine attend a DATA 2000-qualifying 8-hour training program on buprenorphine. SAMHSA maintains a list of upcoming DATA 2000- qualifying buprenorphine training sessions on the SAMHSA Buprenorphine Web site. Additional information about DATA 2000 and buprenorphine also can be obtained by contacting the SAMHSA Buprenorphine Information Center by phone at 866-BUP-CSAT (866-287-2728) or via e-mail at info@buprenorphine.samhsa.gov."

(2) It is recommended that physicians obtain advanced training such as formal ASAM certification or addiction psychiatry fellowship training.

(3) Requirements for INSPECT reviews when prescribing opioids

At the outset of an opioid treatment plan, and at least annually thereafter, a physician prescribing opioids for a patient shall run an INSPECT report on that patient under and document in the patient's chart whether the INSPECT report is consistent with the physician's knowledge of the patient's controlled substance use history.

Section 7. Addressing benzodiazepine use

Introduction: Given the potential lethality of opioids and benzodiazepines, special attention needs to be given to patients taking both classes.
Excerpted from Management of Benzodiazepines in Medication-Assisted Treatment [44]:
"Generally:
1. Individuals must be agreeable to engage in a plan to address their benzodiazepine use before beginning MAT.
2. [*The evidence base does not support the use of chronic*] benzodiazepines in a person presenting for MAT with methadone or buprenorphine is contraindicated. It presents an extremely high risk for adverse drug reaction involving overdose and/or death during the induction process. [*A closely supervised, short-term benzodiazepine taper is indicated in this instance.*]
3. CNS [*central nervous system*] depressant use is not an absolute contraindication for either methadone or buprenorphine, but is a reason for caution because of potential respiratory depression. Serious overdose and death may occur if MAT is administered in conjunction with benzodiazepines, sedatives, tranquilizers, anti- depressants, or alcohol.
4. Individuals who use benzodiazepines, even if used as a part of long-term therapy, should be considered at risk for adverse drug reactions including overdose and death….
6. If a person presenting for MAT will not allow a clinician to coordinate care, he or she [*is not*] appropriate for methadone and/or buprenorphine

Section 8. Managing Relapse

Introduction: Relapse is an anticipated event in the process of recovery. Nonetheless, there are practices that prescribers can adopt that are more likely to promote recovery than others. Best practices to address relapse are detailed here.

Excerpted from APA guidelines [2]: "Because individuals with substance use disorders are often ambivalent about giving up their substance use, it can be useful to monitor their attitudes about participating in treatment and adhering to specific recommendations. These patients often deny or minimize the negative consequences attributable to their substance use; this tendency is often erroneously interpreted by clinicians and significant others as evidence of dishonesty. Even patients entering treatment with high motivation to achieve abstinence will struggle with the reemergence of craving for a substance or preoccupation with thoughts about attaining or using a substance. Moreover, social influences (e.g., substance- using family or friends), economic influences (e.g., unemployment), medical conditions (e.g., chronic pain, fatigue), and psychological influences (e.g., hopelessness, despair) may make an individual more vulnerable to a relapse episode even when he or she adheres to prescribed treatment. For these reasons, it can be helpful for clinicians and patients to anticipate the possibility that the patient may return to substance use and to agree on a corrective plan of action should this occur. If the patient is willing, it can be helpful to involve significant others in preventing the patient's relapse and prepare significant others to manage relapses should they occur.

Supporting patients in their efforts to reduce or abstain from substance use positively reinforces their progress. Overt recognition of patient efforts and successes helps to motivate patients to remain in treatment despite setbacks. Clinicians can optimize patient engagement and retention in treatment through the use of motivational enhancement strategies [45, 46] and by encouraging patients to actively partake in self-help strategies. Monitoring programs, such as EAPs and impaired-physician programs [47-49], can sometimes help patients adhere to treatment.

Early in treatment a clinician may educate patients about cue-, stress-, and substance-induced relapse triggers [50, 51]. Patients benefit from being educated in a supportive manner about relapse risk situations, thoughts, or emotions; they must learn to recognize these as triggers for relapse and learn to manage unavoidable triggers without resorting to substance-using behaviors. Participation in AA or similar self-help group meetings can also support patients' sobriety and help them avoid relapse. Many other strategies can also help prevent relapse. Social skills training is targeted at improving individual responsibility within family relationships, work related interactions, and social relationships. During the early recovery phase, it can be helpful to encourage patients to seek new experiences and roles consistent with a substance-free existence (e.g., greater involvement in vocational, social, or religious activities) and to discourage them from instituting major life changes that might increase the risk of relapse. Facilitating treatment of co-occurring psychiatric and medical conditions that significantly interact with substance relapse is a long- term intervention for maintaining sobriety [52-54]. Therapeutic strategies to prevent relapse have been well studied and include teaching individuals to anticipate and avoid substance-related cues (e.g., assessing individual capacity to avoid relapse in the presence of substance-using peers), training individuals how to monitor their affective or cognitive states associated with increased craving and substance use, behavioral contingency contracting, training individuals in cue extinction and relaxation therapies to reduce the potency of substance-related stimuli and modulate craving intensity, and supporting patients in the development of coping skills and lifestyle changes that support sobriety [55, 56]. Behavioral techniques that enhance the availability and perceived value of social reinforcement as an alternative to substance use or reward for remaining abstinent have also been used [57]. If relapse does occur, individuals should be praised for even limited success and encouraged to continue in or resume treatment. Clinicians may help patients analyze relapses as well as periods of sobriety from a functional and behavioral standpoint and use what is learned to adjust the treatment plan to fit the individual's present needs. For chronically relapsing substance users, medication therapies may be necessary adjuncts to treatment."

Section 9. Obtaining informed consent concerning all available opioid use disorder treatment options, including risks and benefits of each option.

Introduction: The informed consent process should ensure that each patient voluntarily chooses their treatment and that relevant facts concerning the use of the medications (including non-opioid medication treatment options) are clearly and adequately explained, such as follows :

Opioids are drugs that stimulate mu-receptors in the brain to produce a wide range of effects including pain relief, sedation, euphoria, addiction, and, with high enough doses, death. Opioids include heroin, morphine, methadone, oxycodone, hydrocodone, buprenorphine, tramadol and others. An opioid use disorder (i.e. addiction) is diagnosed when opioids are used in a compulsive, uncontrolled way producing negative physical, mental and social consequences. Treatment options for opioid addictions are compared below.

Behavioral Interventions: Behavioral interventions are recommended to accompany any addiction treatment.
Benefits and advantages:
Capable of addressing a host of contexts associated with addiction (e.g., depression or pain)
No medication costs or side effects, except in the case of adolescents, where groups have been shown to worsen prognosis
Risks and downsides:
The long-term chance of quitting opioids is low without taking medication like those listed below.
Group therapies involve some compromise of confidentiality and can be time consuming.

Methadone: Methadone is an opioid dispensed by a government regulated Opiate Treatment Provider (OTP).

Benefits and advantages:

Scientifically proven to reduce withdrawal, illicit opioid relapse, psychiatric, legal, medical, social and financial consequences of opioid addiction.
Clients are monitored closely for progress.

Risks and downsides:
Requires ongoing use of opioids
Requires daily, often early morning visits to the OTP in the first months.
OTPs typically focus on only opioid addiction and do not treat other co-occurring addictions and mental illnesses.
OTP/Methadone treatment is generally not covered by public/private insurance. Only 13 OTP clinics and the Veteran's Administration in Indiana--so may need to drive long distances.
Methadone can cause serious side effects with high doses, or when mixed with alcohol, benzodiazepines, barbiturates or certain muscle relaxants; Can cause irregular heartbeat, cessation of breathing and death.
Stopping methadone, as with any opioid, causes opioid withdrawal sickness. Accidental ingestion by children can be fatal.

Buprenorphine (Suboxone, Subutex, Zubsolv, Bunavail): Buprenorphine is an opioid prescribed by an OTP or a doctor with a special prescribing certification. It has many of the same benefits and risks as methadone. However there are several key differences listed as follows.

Benefits and advantages:
Buprenorphine treatment (outside of an OTP) typically requires fewer treatment appointments than methadone to receive medication.
Buprenorphine treatment is more often covered by public and private insurance. Risk of lethal over dose is much less than with methadone or other opioids.
Babies born to mothers maintained on Buprenorphine have less risk of experiencing NAS.

Risks and downsides:
May not work as well as methadone in certain patients with severe opioid addiction. Lack of highly structured treatment programming with buprenorphine does not serve some people well.

Naltrexone (Revia, Vivitrol): Naltrexone is a prescription drug that blocks the effects of opioids in the brain. Naltrexone comes as a pill that is taken one or two times a day or as a shot given by a nurse once a month. You cannot take opioids for about two weeks before starting naltrexone. Naltrexone is also used to treat alcohol addiction.

Benefits and advantages:
Does not require the use of an opioid to facilitate recovery Increases adherence to psycho-social treatment.
Significantly reduces cravings for opioids.
Will not result in respiratory depression if taken in excess Covered by most insurance plans.
Treats alcohol addiction too.

Risks and downsides:
Naltrexone may cause opioid withdrawal symptoms if started before someone has detoxed from opioids.

Can cause serious liver problems, although this is more likely when taking high doses of the oral form. Opioid pain medications will not work as well when taking naltrexone. The injection can cause some discomfort, rarely could become infected. Individuals can still overdose on opioids, while taking naltrexone.

Should not be started during pregnancy.

This information has been reviewed with the client, by the signing physician.

Signature of Client: date:

Signature of Physician: date:

Section 10. Drug Testing

Introduction: Testing biological samples for the presence of drugs of abuse is an essential part of the treatment of OUDs. Best practices of drug screening are detailed here.

Excerpted from APA[2]: "Urine drug testing, or other reliable biological tests for the presence of drugs, during the initial evaluation and frequently throughout treatment, is highly recommended. Results from some studies have indicated that more intensive monitoring of substance use may increase recovery rates from a substance use disorder…There are a variety of toxicology tests available, some with greater and lesser reliability and validity. Urine testing is useful for detecting substance use over the preceding 5-day period for common substances of abuse (cocaine, opiates, cannabis, amphetamines, benzodiazepines, and PCP); however, certain opioids (buprenorphine, oxycodone, hydrocodone, and fentanyl) cannot be detected with routine methods and require special assays. [*It is important to screen for the metabolites of the prescribed opioid agonist (e.g. norbuprenorphine), to ensure compliance with the treatment. Point of care testing (e.g., urine testing) is needed to make rapid clinical decisions, supplemented by "send out," confirmatory laboratory values.*] The person who is interpreting these labs should be very familiar with the methodology and the reliability.
There is little research on the optimal frequency of testing, [*however, random drug testing is ideal.*]….The frequency of drug testing will be determined by a number of factors, including the stability of the patient, the type of treatment, the treatment setting, and the half-life of drugs in the matrix being tested. Patients will likely require more testing early in treatment or during periods of relapse. Patients participating in office based treatment with buprenorphine may be tested at each office visit.

Opioids are detectable in the urine for 1–3 days after use. A negative urine test combined with no history of withdrawal may indicate a lack of physical dependence.

However, a negative urine test does not rule out opioid use, disorder, or physical dependence. Urine testing is also helpful to identify
(1) use of other psychoactive substances.
(2) If a patient tests positive for an illegal drug…or a controlled substance that the patient is not taking as part of the treatment plan, then the provider needs to review the treatment plan and consider changes with the goal of opioid abstinence."

Section 11. Pregnant Women with OUDs

Introduction: Pregnant women have unique needs and require treatment customized to their situation. Best practices for their treatment are highlighted here.
(Excerpted from ASAM guidelines [1]
"(1) The first priority in "treating" pregnant women for opioid use disorder should be to identify emergent or urgent medical conditions that require immediate referral for clinical evaluation.
(2) A medical examination and psychosocial assessment is recommended when evaluating pregnant women for opioid use disorder.
(3) Obstetricians and gynecologists should be alert to signs and symptoms of opioid use disorder. Pregnant women with opioid use disorder are more likely to seek prenatal care late in pregnancy, miss appointments, experience poor weight gain, or exhibit signs of withdrawal or intoxication.

(4) [*As with all patients with OUDs,*] psychosocial treatment is [*strongly*] recommended in the treatment of pregnant women with opioid use disorder.

(5) Counseling and testing for HIV should be provided in accordance with state law. Tests for hepatitis B and C and liver function are also suggested. Hepatitis A and B vaccination is recommended for those whose hepatitis serology is negative.

(6) Urine drug testing may be used to detect or confirm suspected opioid and other drug use with informed consent from the mother, realizing that there may be adverse legal and social consequences of her use. State laws differ on reporting substance use during pregnancy. Laws that penalize women for use and for obtaining treatment serve to prevent women from obtaining prenatal care and worsen outcomes.

(7) Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine mono-product rather than withdrawal management or abstinence.

(8) Care for pregnant women with opioid use disorder should be co-managed by an obstetrician and an addiction specialist physician. Release of information forms need to be completed to ensure communication among healthcare providers.

(9) Treatment with [*buprenorphine or*] methadone *[(within a licensed Opioid Treatment Program)*] should be initiated as early as possible during pregnancy.

(10) Hospitalization during initiation of methadone and treatment with buprenorphine may be advisable due to the potential for adverse events, especially in the third trimester.

(14) Clinicians should be aware that the pharmacokinetics of [*buprenorphine*] are affected by pregnancy….Increased or split doses may be needed as pregnancy progresses. After child birth, doses may need to be adjusted.

(15) Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. Whereas there is evidence of safety, there is insufficient evidence to recommend the combination buprenorphine/ naloxone formulation.

(16) If a woman becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue the medication if the patient and doctor agree that the risk of relapse is low. If the patient is highly concerned about relapse and wishes to continue naltrexone, she should be informed about the risks of staying on naltrexone and provide her consent for ongoing treatment. If the patient wishes to discontinue naltrexone, but then reports relapse to opioid use, it may be appropriate to consider treatment with methadone or treatment with buprenorphine.

(17) Naloxone is not recommended for use in pregnant women with opioid use disorder except in situations of life-threatening overdose.

(18) Mothers receiving methadone and buprenorphine monoproduct for the treatment of opioid use disorders should be encouraged to breastfeed.

(19) [*Naltrexone may be appropriate for a mother after delivery who is capable of detoxification and at risk of relapse.*]

Methadone Versus Buprenorphine
The discussion and decision for medication should be reviewed with the patient and documented in her chart. For women who are pregnant or breastfeeding, opioid agonist treatment with methadone or buprenorphine is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on perinatal care and parenting of young children. Methadone is the accepted standard of care for use during pregnancy; however, buprenorphine monoproduct is a reasonable alternative and also has some advantages over methadone. Infants born to mothers treated with buprenorphine had shorter hospital stays (10 vs. 17.5 days), had shorter treatment durations for neonatal abstinence syndrome (NAS) (4.1 vs. 9.9 days), and required a lower cumulative dose of morphine (1.1 vs. 10.4 mg) compared to infants born to mothers on treatment with methadone.

Combination Buprenorphine/Naloxone
There is some evidence suggesting that buprenorphine/ naloxone is equivalent in safety and efficacy to the monoproduct for pregnant women. At present, however, this evidence is insufficient to recommend the combination buprenorphine/naloxone formulation in this population."

References

1. Sandra Comer, P., et al., National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. 2015, American Society of Addiction Medicine. p. 1-66.
2. WORK GROUP ON SUBSTANCE USE DISORDERS, A.P.A., PRACTICE GUIDELINE for the Treatment of Patients With Substance Use Disorders. 2006.
3. Charney, D.S., et al., The clinical use of clonidine in abrupt withdrawal from methadone. Effects on blood pressure and specific signs and symptoms. Arch Gen Psychiatry, 1981. 38(11): p. 1273- 7.
4. Kleber, H.D., et al., Clonidine in outpatient detoxification from methadone maintenance. Arch Gen Psychiatry, 1985. 42(4): p. 391-4.
5. Cami, J., et al., Efficacy of clonidine and of methadone in the rapid detoxification of patients dependent on heroin. Clin Pharmacol Ther, 1985. 38(3): p. 336-41.
6. Jasinski, D.R., R.E. Johnson, and T.R. Kocher, Clonidine in morphine withdrawal. Differential effects on signs and symptoms. Arch Gen Psychiatry, 1985. 42(11): p. 1063-6.
7. Collins, E.D., et al., Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. JAMA, 2005. 294(8): p. 903-13.
8. O'Connor, P.G., et al., Ambulatory opiate detoxification and primary care: a role for the primary care physician. J Gen Intern Med, 1992. 7(5): p. 532-4.
9. Collins ED and K. H, Opioids: detoxification, in The American Psychiatric Publishing Textbook of Substance Abuse Treatment, K. Galanter M, Editor. 2004, American Psychiatric Publishing: Washington DC. p. 265-289.
10. HB, G. and A. H, Opioid analgesics, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th editon, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, Hardman JG, Limbird LE, and G. AG, Editors. 2001, McGraw-Hill: New York. p. 51.
11. Martin, W.R., Naloxone. Ann Intern Med, 1976. 85(6): p. 765-8.
12. S, D., Opioids, in Emergency Medicine: A Comprehensive Study Guide, K.G. Tintinalli JE and S. JS, Editors. 2004, McGraw-Hill: New York. p. 1071-1074.
13. Berkowitz, R.L., B.W. Bonta, and J.E. Warshaw, The relationship between premature rupture of the membranes and the respiratory distress syndrome. Am J Obstet Gynecol, 1976. 124(7): p. 712-8.
14. Watson, W.A., et al., Opioid toxicity recurrence after an initial response to naloxone. J Toxicol Clin Toxicol, 1998. 36(1-2): p. 11-7.
15. Hubbard RL, Marsden ME, and R. JV:, Drug Abuse Treatment: A National Study of Effectiveness.
Chapel Hill, University of North Carolina Press, 1989.
16. Simpson, D.D., G.W. Joe, and S.A. Bracy, Six-year follow-up of opioid addicts after admission to treatment. Arch Gen Psychiatry, 1982. 39(11): p. 1318-23.
17. Simpson, D.D., L.J. Savage, and M.R. Lloyd, Follow-up evaluation of treatment of drug abuse during 1969 to 1972. Arch Gen Psychiatry, 1979. 36(7): p. 772-80.
18. Simpson, D.D. and S. Sells, Opioid Addiction and Treatment: A 12-Year Follow-Up. 1990.
19. Nyswander, M., The treatment of drug addiction. Med Clin North Am, 1958. 42(3): p. 815-22.
20. Woody, G.E., et al., Psychotherapy for opiate addicts. Does it help? Arch Gen Psychiatry, 1983.

40(6): p. 639-45.
21. Woody, G.E., et al., Sociopathy and psychotherapy outcome. Arch Gen Psychiatry, 1985. 42(11): p. 1081-6.
22. Woody, G.E., et al., Twelve-month follow-up of psychotherapy for opiate dependence. Am J Psychiatry, 1987. 144(5): p. 590-6.
23. Woody, G.E., et al., Psychotherapy in community methadone programs: a validation study. Am J Psychiatry, 1995. 152(9): p. 1302-8.
24. Woody, G.E., A.T. McLellan, and C.P. O'Brien, Treatment of behavioral and psychiatric problems associated with opiate dependence. NIDA Res Monogr, 1984. 46: p. 23-35.
25. O'Neill, K., et al., Evaluation of a cognitive-behavioural intervention for pregnant injecting drug users at risk of HIV infection. Addiction, 1996. 91(8): p. 1115-25.
26. McAuliffe, W.E., A randomized controlled trial of recovery training and self-help for opioid addicts in New England and Hong Kong. J Psychoactive Drugs, 1990. 22(2): p. 197-209.
27. McLellan, A.T., et al., The effects of psychosocial services in substance abuse treatment. JAMA, 1993. 269(15): p. 1953-9.
28. Silverman, K., et al., Sustained cocaine abstinence in methadone maintenance patients through voucher-based reinforcement therapy. Arch Gen Psychiatry, 1996. 53(5): p. 409-15.
29. Silverman, K., et al., Broad beneficial effects of cocaine abstinence reinforcement among methadone patients. J Consult Clin Psychol, 1998. 66(5): p. 811-24.
30. Iguchi MY, et al., Contingent reinforcement of group participation versus abstinence in methadone maintenance program. Exp Clin Psychopharmacol, 1996. 4: p. 7.
31. Stitzer, M. and G. Bigelow, Contingency management in a methadone maintenance program: availability of reinforcers. Int J Addict, 1978. 13(5): p. 737-46.
32. Stitzer, M.L., et al., Effect of methadone dose contingencies on urinalysis test results of polydrug- abusing methadone-maintenance patients. Drug Alcohol Depend, 1986. 18(4): p. 341-8.
33. Stitzer, M.L., M.Y. Iguchi, and L.J. Felch, Contingent take-home incentive: effects on drug use of methadone maintenance patients. J Consult Clin Psychol, 1992. 60(6): p. 927-34.
34. Carroll, K.M., et al., Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. Arch Gen Psychiatry, 2001. 58(8): p. 755-61.
35. Carroll, K.M., et al., Contingency management to enhance naltrexone treatment of opioid dependence: a randomized clinical trial of reinforcement magnitude. Exp Clin Psychopharmacol, 2002. 10(1): p. 54-63.
36. Grabowski, J., et al., Effects of contingent payment on compliance with a naltrexone regimen. Am J Drug Alcohol Abuse, 1979. 6(3): p. 355-65.
37. Greenstein R, Fudala PJ, and O.B. CP, Alternative pharmacotherapies for opiate addiction, in Substance Abuse: A Comprehensive Textbook, Lowinson JH, et al., Editors. 1997, Williams and Wilkins: New York. p. 415-424.
38. Meyer, R.E., et al., A behavioral paradigm for the evaluation of narcotic antagonists. Arch Gen Psychiatry, 1976. 33(3): p. 371-7.
39. Preston, K.L., et al., Improvement in naltrexone treatment compliance with contingency management. Drug Alcohol Depend, 1999. 54(2): p. 127-35.
40. Rounsaville, B.J., Can psychotherapy rescue naltrexone treatment of opioid addiction? NIDA Res Monogr, 1995. 150: p. 37-52.

41. Khantzian EJ, Halliday KS, and M. WE, Addiction and the Vulnerable Self: Modified Dynamic Group Therapy for Substance Abusers. 1990.
42. Fals-Stewart W, O'Farrell TJ, and B. GR, Behavioral couples therapy for male methadone maintenance patients: effects on drug using behavior and relationship adjustment. Behavioral therapy, 2001. 32: p. 391-411.
43. Fals-Stewart, W. and T.J. O'Farrell, Behavioral family counseling and naltrexone for male opioid- dependent patients. J Consult Clin Psychol, 2003. 71(3): p. 432-42.
44. Management of Benzodiazepines in Medication-Assisted Treatment. 2013, Institute for Research, Evaluation and Training in Addictions with Support from Community Care Behavioral Health Organization. p. 1-26.
45. Connors, G.J., K.S. Walitzer, and K.H. Dermen, Preparing clients for alcoholism treatment: effects on treatment participation and outcomes. J Consult Clin Psychol, 2002. 70(5): p. 1161-9.
46. Miller WR and R. S, Motivational Interviewing: Preparing People for Change. 2002, New York: Guildford.
47. Chan, K.K., C. Neighbors, and G.A. Marlatt, Treating addictive behaviors in the employee assistance program: implications for brief interventions. Addict Behav, 2004. 29(9): p. 1883-7.
48. Domino, K.B., et al., Risk factors for relapse in health care professionals with substance use disorders. JAMA, 2005. 293(12): p. 1453-60.
49. Zarkin, G.A., J.W. Bray, and J. Qi, The effect of Employee Assistance Programs use on healthcare utilization. Health Serv Res, 2000. 35(1 Pt 1): p. 77-100.
50. Lowman, C., J. Allen, and R.L. Stout, Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. The Relapse Research Group. Addiction, 1996. 91 Suppl: p. S51-71.
51. Stewart, J., Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug- taking. J Psychiatry Neurosci, 2000. 25(2): p. 125-36.
52. Substance Abuse and Mental Health Services Administration: Report to Congress on the Prevention and Treatment of Co-Occurring Substance Abuse Disorders and Mental Disorders., U.D.o.H.a.H. Services, Editor. 2002: Washinton DC.
53. Galanter, M., Network therapy for addiction: a model for office practice. Am J Psychiatry, 1993. 150(1): p. 28-36.
54. Khantzian, E.J., The primary care therapist and patient needs in substance abuse treatment. Am J Drug Alcohol Abuse, 1988. 14(2): p. 159-67.
55. Us Department of Health and Human Services: Brief Interventions and Brief Therapies for Substance Abuse: Treatment Improvement Protocol (TIP) Series, U.S.A.a.M.H.S. Administration, Editor. 1999, DHHS Publication: Rockville, Md.
56. Daley DC and M. GA, Relapse prevention: cognitive and behavioral interventions, in Substance Abuse: A Comprehensive Textbook, Lowinson JH, et al., Editors. 1992, Williams and Wilkins: Baltimore, Md. p. 533-542.
57. Miller WR and H. RK, The effectiveness of alcoholism treatment: what research reveals, in Treating Addictive Behaviors: Processes of Change. 1986: p. 53.