

# The Outpatient Treatment Manual for the Care of Opioid-Dependent Pregnant Women with Buprenorphine



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The goal of this project was to develop a clinical treatment protocol for the care of opioid dependent pregnant women using buprenorphine with an emphasis on the inclusion of the latest evidence based medicine. It is also based on the experience of Drs. O'Connor and Alto who created an integrated medical and behavioral health treatment program within a family medicine residency in a predominantly rural and underserved area in Maine. Well over 100 pregnant women have now been cared for in this integrated program. These guidelines are not intended to replace providers' clinical judgment and clinicians are encouraged to collaborate and seek consultation from obstetric, pediatric and addiction medicine specialists as indicated.

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## **Introduction**

For more than 40 years, methadone has been the standard of care in the treatment of pregnant women with opioid use disorders. However, a growing body of evidence suggests that buprenorphine is a safe and effective alternative and many now advocate that it should also be a first line therapy during pregnancy (Alto & O'Connor, 2011; Jones et al., 2010). In contrast to methadone, buprenorphine is associated with fewer maternal medical complications and overdoses and a shorter duration of infant hospitalization (Bell et al., 2009; Holbrook et al., 2012; Jones et al., 2005; Jones et al., 2010). Infants of mothers treated with buprenorphine during pregnancy have a similar or lower frequency and/or severity of neonatal abstinence syndrome (NAS) when compared to those born to mothers maintained on methadone during pregnancy (Bell et al., 2009; Fischer et al., 2006; Gaalema et al., 2012; Jones et al., 2005; Jones et al., 2010; Lejeune et al., 2006).

## **Overview of opioid use disorders**

Opioid use disorders are a growing public health concern in the United States. The 12-month prevalence of individuals with opioid use disorders is approximately 0.37% among adults age 18 years and older (Compton et al., 2007). This may be an underestimate because of the large number of incarcerated individuals with opioid use disorders (Compton et al., 2010). Rates are higher in males than in females (0.49% vs. 0.26%), with the male-to-female ratio typically being 1.5:1 for opioids other than heroin (i.e., prescription analgesics) and 3:1 for heroin. Female adolescents may have a higher likelihood of developing opioid use disorders (Wu et al., 2009). The prevalence decreases with age, with the prevalence highest (0.82%) among adults age 29 years or younger, and decreasing to 0.09% among adults age 65 years and older. Among adults, the prevalence of opioid use disorders is lower among African Americans at 0.18% and overrepresented among Native Americans at 1.25%. It is close to average among whites (0.38%), Asian or Pacific Islanders (0.35%), and Hispanics (0.39%) (Wu et al., 2009). While the

12-month prevalence of heroin use disorders is low (0.1%) among US individuals age 12 to 17 years, the prevalence of opioid use disorders associated with the misuse of narcotic analgesics is about 1.0%; this highlights the importance of narcotic analgesics as a group of substances with potentially significant health consequences (US Substance Abuse and Mental Health Services Administration, 2011).

Individuals living in economically deprived areas are overrepresented among individuals with opioid use disorders. Over time, opioid use disorders are increasingly seen among white, middle-class individuals, especially females, suggesting that differences in use reflect the availability of opioid drugs and that other social factors may impact prevalence.

## **Development of opioid use disorders and prognostic factors**

Opioid use disorders can begin at any age but problems associated with opioid use are most commonly first observed in the late teens or early 20s. Once an individual develops an opioid use disorder, it usually continues over a period of many years, even though brief periods of abstinence are frequent. In treated populations, relapse following abstinence is common. Even though relapses do occur, and some long-term mortality rates may be as high as 2% per year, about 20% to 30% of individuals with opioid use disorders achieve long-term abstinence (Price, Risk, & Spitznagel, 2001). Increasing age is associated with a decrease in prevalence as a result of early mortality and the remission of symptoms after age 40. However, many individuals continue have clinical presentations that meet the criteria for an opioid use disorder for decades (Hser et al., 2007).

The risk for an opioid use disorder can be related to individual, family, peer, and social environmental factors but, within these domains, genetic factors play a particularly important role both directly and indirectly (Kendler et al., 2003; Tsuang et al., 1998). For instance, impulsivity and novelty seeking behaviors are individual temperaments that relate to the propensity to develop a substance use disorder and may be genetically determined. Peer factors may relate to genetic predisposition in terms of how an individual selects his or her environment.

## **Complications of opioid use disorders in pregnancy**

Nearly one-third of those being treated for opioid use disorders in the US are women of childbearing age (Johnson, Jones, & Fischer, 2003). It is critical for pregnant women with opioid use disorders to be treated properly both to reduce fetal exposure to illicit drugs and to prevent fetal withdrawal if opioid use is abruptly terminated. The adverse maternal-fetal effects of opioid abuse and misuse during pregnancy include intrauterine growth restriction, placental insufficiency, preterm rupture of membranes, premature delivery, postpartum hemorrhage and perinatal mortality (Bolnick & Rayburn, 2003; Kaltenbach, Berghella, & Finnegan, 1998). Beyond the physical implications, treatment of an opioid use disorder during pregnancy improves the mother's social situation and likely reduces exposure to criminal activity associated with the drug culture. During pregnancy, outpatient treatment programs are more cost-effective than either inpatient treatment or opioid detoxification (Daley et al., 2001)

Providers caring for pregnant women need to be familiar with both the clinical presentation of an opioid use disorder and/or acute opioid withdrawal and also with treatment resources in their area. Pregnant women who are dependent upon opioids should expect priority admission at most treatment facilities. Many women have partners with opioid use disorders and pregnancy may present the ideal time for both to enter treatment (Fischer, 2000). Ideally, programs will also provide support and medication assisted treatment for these partners.

## **Screening for substance use during pregnancy**

All pregnant women should be screened for substance use during pregnancy at entry into prenatal care and again in the mid-second trimester (The Snuggle ME Project, 2012). It is critical to screen in a sensitive and non-judgmental manner as pregnant women are often fearful of being identified because of potential social and legal consequences including judgment from providers, maternal feelings of failure, and reporting to child protective services (Roberts & Nuru-Jeter, 2010). Pregnant women with substance use disorders sometimes avoid or disengage from prenatal care due to fear of being identified.

When screening for substance use disorders, the provider should remind the patient that all women are screened for substance use disorders during pregnancy to identify factors that may put the fetus and mother at risk for medical complications. Screening should always be done in private and not in the presence of family and/or partners. Several screening instruments have been developed for use in pregnant women although additional research is needed to identify and validate optimal instruments. The American College of Obstetricians and Gynecologists (ACOG) and the American Society of Addiction Medicine (ASAM) (2012) advocate the use of the 4Ps screening instrument and the CRAFFT questionnaire (for women 26 years old or younger) during pregnancy. The 4 Ps screening instrument is Appendix B and the CRAFFT questionnaire is Appendix C in this treatment manual.

If the clinician observes any of the physical signs and symptoms associated with substance use during the course of pregnancy, the patient should be rescreened. This may include track marks and/or signs of acute opioid intoxication (e.g., pinpoint pupils, loss of alertness, diminished respirations) or acute opioid withdrawal (e.g., dilated pupils, diffuse muscle aches, increased agitation, sweating, tearing/runny nose). Erratic patient behavior and/or late entry into prenatal care or irregular prenatal care may be suggestive of substance use and warrant additional interviewing. Although urine toxicology testing can be an important clinical tool once a woman is enrolled in treatment, ACOG and ASAM (2012) do not recommend its use as the primary screening instrument. If urine toxicology testing is performed, it should only be done in accordance with state laws and with the patient's informed consent.

## **Definition of opioid use disorder**

Clinicians providing obstetrical care to pregnant women with substance use disorders need to be able to distinguish between intermittent substance misuse and physical dependence as it may influence the level and type of care required. According to the American Psychiatric Association DSM V (2013), the diagnostic criterion for an opioid use disorder is met when a problematic pattern of opioid use leading to



clinically significant impairment or distress, as manifested by at least two of the following, occurs within a 12-month period:

- Opioids are taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Tolerance, as defined by either of the following:
  - A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
  - A markedly diminished effect with continued use of the same amount of an opioid.
  - Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
- Withdrawal, as manifested by either of the following:
  - The characteristic opioid withdrawal syndrome.
  - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

- Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

## **Diagnostic features of opioid use disorder**

Opioid use disorder includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition. For example, an individual prescribed narcotic analgesic for pain relief at adequate dosing may use significantly more than prescribed despite adequate pain relief. Individuals with opioid use disorder tend to develop such regular patterns of compulsive drug use that daily activities are planned around obtaining and administering opioids. Opioids are usually purchased on the illegal market but may also be obtained from health care providers by falsifying or exaggerating general medical problems or by receiving simultaneous prescriptions from several providers.

Most individuals with an opioid use disorder have significant levels of tolerance and will experience withdrawal on abrupt discontinuation of opioid substances. Individuals with opioid use disorders often develop conditioned responses to drug-related stimuli (e.g., craving on seeing any heroin powder-like substance) - a phenomenon that occurs with most drugs and cause intense psychological changes. These responses probably contribute to relapse, are difficult to extinguish, and typically persist long after detoxification is completed (Fatseas et al. 2011). Other associated features that can support the diagnosis of an opioid use disorder may include a history of drug-related crimes (e.g., possession or distribution of drugs, forgery, burglary, robbery, larceny, receiving stolen goods). Marital difficulties (including divorce), unemployment, and irregular employment are often associated with opioid use disorders at all socioeconomic levels.

## **Infectious diseases and other health complications**

Opioid use is associated with a lack of mucous membrane secretions, causing dry mouth and nose. Slowing of gastrointestinal activity and a decrease in gut motility can produce severe constipation. Visual acuity may be impaired as a result of pupillary constriction with acute administration. In individuals who inject opioids, sclerosed veins (“tracks”) and puncture marks on the lower portions of the upper extremities are common. Veins sometimes become so severely sclerosed that peripheral edema develops, and individuals switch to injecting in veins in the legs, neck, or groin. When these veins become unusable, individuals often inject directly into their subcutaneous tissue (“skin-popping”), resulting in cellulitis, abscesses, and circular-appearing scars from healed skin lesions. Tetanus, anthrax and clostridium botulinum infections are relatively rare but extremely serious consequences of injecting opioids, especially with the use of contaminated needles. Infections may also occur in other organs and include bacterial endocarditis, hepatitis, and HIV infection.

Previous or current history of intravenous drug use implies that the patient may have been exposed to the hepatitis C virus and, depending upon the population, infection rates can be as high as 90%. Providers should add hepatitis C antibody testing to routine prenatal screening. Women are often hesitant to disclose intravenous drug use due to stigma; therefore, it is likely prudent to screen all women with a history of substance use for the virus. The risk of vertical transmission of the hepatitis C virus to the fetus is relatively low (about 5%) (Robinson, 2008) and breastfeeding is not contraindicated; however, providers should be aware that the risk of transmission is increased if the patient’s nipples are cracked and bleeding. Buprenorphine does not appear to have adverse hepatic effects on pregnant women even those who are carriers of the hepatitis C virus (McNicholas et al., 2012). However, liver enzymes are often mildly elevated, either as a result of resolving hepatitis or toxic injury to the liver due to contaminants that have been mixed with the injected opioid.

The prevalence of HIV infection can be high among individuals who inject drugs, a large proportion of whom are individuals with an opioid use disorder. HIV infection rates have been reported to

be as high as 60% among heroin users in some areas of the United States. However, the incidence may also be 10% or less in other areas, especially those where access to clean injection material and paraphernalia is facilitated (Fatseas et al., 2011).

Women with a history of substance use disorders are also at an increased risk for sexually transmitted infections (Horrigan et al., 2000). An ongoing substance use disorder places the woman at risk for unsafe sexual practices and may lead to situations in which sex is traded for drugs. At a minimum, screening for sexually transmitted infections including HIV, hepatitis B and C, chlamydia, gonorrhea and syphilis should occur at entry into prenatal care. These labs can be repeated again in the third trimester if risky behaviors have continued during pregnancy as there may be a delay between exposure and diagnosis (Winklbaur et al., 2008).

A history of incarceration or homelessness may increase a woman's risk of tuberculosis and many experts recommend tuberculin skin testing (Winklbaur et al., 2008). Tuberculosis is a particularly serious problem among individuals who use drugs intravenously, especially those who are dependent on heroin. However, infection is usually asymptomatic and detected only by the presence of a positive tuberculin skin test. However, cases of active tuberculosis have been found, especially among those who are infected with HIV. These individuals often have a newly acquired infection but also are likely to experience reactivation of a prior infection because of impaired immune function.

Individuals who sniff heroin or other opioids into the nose ("snorting") often develop irritation of the nasal mucosa, sometimes accompanied by perforation of the nasal septum. Difficulties in sexual functioning are common. Males often experience erectile dysfunction during intoxication or chronic use. Females commonly have disturbances of reproductive function and irregular menses.

Because of a variety of infections including cellulitis, hepatitis, HIV, tuberculosis, and endocarditis, opioid use disorders are associated with a mortality rate as high as 1.5% to 2% per year. Deaths are also associated with acute drug overdoses, accidents, injuries, and other general medical complications.

## **Co-occurring mental health disorders**

Pregnant women with substance use disorders have a high prevalence (often as many as 65%) of co-existing mental health diagnoses which may impact their ability to obtain treatment services (Benningfield et al., 2010). More than two thirds of the pregnant women treated in our program have co-occurring mental health diagnoses. The most common diagnoses are anxiety, depression, bipolar disorder and post-traumatic stress disorder. Other authors similarly report that pregnant women with substance use disorders are highly likely to have history of severe depression and/or have been a victim of physical and/or sexual abuse (Horrigan, Schroeder, & Schaffer, 2000). Pregnant women with opioid use disorders and co-occurring anxiety are more likely to discontinue treatment during pregnancy suggesting that these women should be carefully monitored (Benningfield et al., 2012).

Pregnant women with a history of major depressive disorder, generalized anxiety disorder or post-traumatic stress disorder also tend to have higher scores on the addiction severity index (Benningfield et al., 2010). Similar to the risk generally observed for all substance use disorders, opioid use disorder is associated with a heightened risk for suicide attempts and completed suicides. Particularly notable are both accidental and deliberate opioid overdoses. Repeated opioid intoxication or withdrawal may be associated with severe depression that, although temporary, can be intense enough to lead to suicide attempts and completed suicides.

It is critical to be able to distinguish co-occurring mental health diagnoses from opioid-induced mental health disorders. Opioid-induced disorders may be characterized by symptoms (e.g., depressed mood) that resemble primary mental disorders (e.g., persistent depressive disorder vs. opioid-induced depressive disorder with onset during intoxication). Individuals with opioid use disorder are at risk for the development of mild to moderate depression that meets the symptomatic and duration criteria for persistent depressive disorder (dysthymia) or, in some cases, for major depressive disorder (Compton et al., 2005). These symptoms may represent an opioid-induced depressive disorder or an exacerbation of a preexisting primary depressive disorder. Periods of depression are especially common during chronic

intoxication or in association with physical or psychosocial stressors that are related to the opioid use disorder. It is often easier to make this assessment after the patient is stabilized on medication assisted treatment. Insomnia is common, especially during withdrawal. Opioids are less likely to produce symptoms of mental disturbance than are most other drugs of abuse. Opioid intoxication and opioid withdrawal are distinguished from the other opioid-induced disorders because the symptoms in these latter disorders predominate and are severe enough to warrant independent clinical attention.

## **Barriers to treatment of substance use disorders during pregnancy**

Limited financial resources, a lack of transportation and social supports in addition to child care requirements for existing children are barriers to treatment in pregnant women with substance use disorders. Early referral to social services and local community support agencies can often help address some of these concerns. Social stigma, the fear of losing custody of her children, and low-levels of self-esteem and education may also reduce the likelihood of seeking or accepting treatment.

A previous history of exposure to violence is also common among opioid dependent pregnant women. Velez et al. (2006) studied the history of violence in women with substance use disorders and found that their rates of lifetime abuse was 72.7% for physical abuse, 71.3% for emotional abuse and 44.5% for sexual abuse. Abuse rates remained high during the current pregnancy, ranging from 40.9% for emotional abuse to 20.0% for physical abuse to 7.1% for sexual abuse (Velez et al., 2006). These factors highlight the need for both substance use and mental health counseling during the course of the pregnancy as well as the importance of routine screening for exposure to violence in this at-risk population.

Non-adherence to treatment is a common complication in caring for pregnant women with substance use disorders. The clinician should be constantly assessing the patient's position on the recovery spectrum and should feel comfortable providing motivational interviewing as appropriate. Sometimes non-adherence to treatment is related to external factors such as transportation challenges or

limited social supports. The clinician must be knowledgeable about local community resources and/or have access to a social worker or other professional who can provide referrals to these agencies.

## **Substance abuse treatment**

Substance abuse treatment linked with prenatal care improves prenatal outcomes, with decreased risks of preterm delivery (odds ratio (OR) = 2.1), placental abruption (OR = 6.8) and intrauterine fetal demise (OR=16.2) when compared to pregnant women who screen positive but do not undergo treatment (Goler et al., 2008). Women enrolled in integrated prenatal and substance abuse treatment are less likely to give birth to low birth weight infants and their infants are about half as likely to be admitted to a neonatal intensive care unit when compared to infants born to mothers who enrolled in treatment postpartum (Sweeney et al., 2000). Women receiving substance abuse treatment and prenatal care in the same setting are less likely to deliver low birth weight or preterm infants (Armstrong et al., 2003). Substance abuse treatment during pregnancy is also associated with important social implications. Infants born to women enrolled in treatment are more likely to be discharged to the care of their mother and remain in the care of their mother at one year of age than those not receiving treatment (Meyer et al., 2012). Because of these benefits, some clinicians and insurance companies require the woman's participation in an intensive outpatient program (IOP) or inpatient/residential care during part or all of pregnancy.

Psychosocial interventions have been shown to improve patient outcomes in substance abuse treatment. Enrollment in addiction counseling has been associated with increased retention in treatment when buprenorphine is provided in a primary care setting (Stein, Cioe, & Friedman, 2005). The combination of cognitive behavioral therapy and contingency management has been associated with particularly high effect sizes (Dutra et al., 2008). Cognitive behavioral therapy may be readily available in a variety of settings. Contingency management often involves monetary incentives for negative urine drug screens which may present more of a challenge within treatment networks (Dutra et al., 2008).

In early pregnancy, frequent visits, often weekly, are required to assess mental health co-morbidities and stability in substance abuse treatment. As the pregnancy progresses, these visits can be spaced out if the patient has stabilized in treatment, particularly as obstetrical visits become more frequent.

## **Pharmacology of buprenorphine**

Buprenorphine is a partial-agonist at the mu opioid receptor. It is administered sublingually for the treatment of opioid use disorders. Maximum concentration in the plasma occurs 40 minutes to 3.5 hours after administration (Elkader & Sproule, 2005). The medication is highly lipid soluble and is metabolized via the CYP3A4 pathway into its primary metabolite, norbuprenorphine (Elkader & Sproule, 2005). Important drug-drug interactions can exist especially with protease inhibitors used in the treatment of HIV infection as well as azole antifungals (Elkader & Sproule, 2005). Concomitant use of buprenorphine and benzodiazepines has been associated with adverse events, including death, most likely from a synergistic reaction resulting in respiratory depression (Reynaud et al., 1998).

## **Prescriptive authority of buprenorphine**

DATA 2000 (Title XXXV, Section 3502 of the Children's Health Act of 2000) permits "qualifying physicians" to prescribe FDA-approved medications for use in the maintenance and detoxification of patients with opioid use disorders (US Department of Health and Human Services, 2013). To become a qualified physician, those not certified in addiction medicine must complete no fewer than eight hours of additional training in the treatment of patients with opioid use disorders, have a Drug Enforcement Administration (DEA) license, and have the capacity to refer patients to counseling. DATA 2000 allows qualifying physicians to treat no more than 30 patients with buprenorphine at a time. However, following a 2006 amendment to the Controlled Substances Act, physicians have been able to



file a “notice of intent” to prescribe buprenorphine for up to 100 patients as long as at least one year has passed since being granted initial prescriptive approval (US Department of Health and Human Services, 2013).

Buprenorphine is the only Schedule III medication that existing laws permit only physicians to prescribe (O’Connor, 2011). Any clinician with prescriptive authority for Schedule III medications can prescribe buprenorphine to prevent opioid withdrawal in a hospitalized patient who is enrolled in medication assisted treatment with buprenorphine. Methadone for the treatment of addiction is dispensed only through federally licensed and regulated clinics. Methadone clinics are often unevenly distributed geographically and this can restrict the use and availability of methadone in the treatment of addiction.

## **Decision to use methadone or buprenorphine during pregnancy**

The decision between using methadone or buprenorphine in the maintenance of opioid use disorders during pregnancy can be difficult. It is an individualized choice that is best made in collaboration with the patient. While methadone continues to be the standard of care during pregnancy, a growing body of evidence suggests that buprenorphine is a safe alternative and many now believe it should be a first line therapy (Alto & O’Connor, 2011; Jones et al, 2010). In contrast to methadone, buprenorphine is associated with fewer maternal medical complications (e.g., preterm labor 14.9% vs. 1.8%,  $p=0.04$ ) and overdoses (RR 4.25, 95% CI 1.03-17.54) and a shorter duration of infant hospitalization (17.5 days vs. 10.0 days,  $p<0.0091$ ) (Bell et al., 2009; Holbrook et al., 2012; Jones et al., 2005; Jones et al., 2010). Compared to infants exposed to methadone in utero, infants of mothers treated with buprenorphine during pregnancy have a similar or lower frequency and/or severity of neonatal abstinence syndrome (NAS) (e.g., less morphine required to treat NAS, 10.4 mg vs. 1.1 mg,  $p<0.0091$ ; shorter duration of treatment for NAS, 9.9 days vs. 4.1 days,  $p<0.003$ ) (Bell et al., 2009; Fischer et al., 2006; Gaalema et al., 2012; Jones et al., 2005; Jones et al., 2010; Lejeune et al., 2006) and are less likely to experience respiratory distress at delivery (18.9% vs. 5.3%,  $p=0.05$ ) (Holbrook et al., 2012). Jansson et

al. (2011) found that, when compared to methadone exposed fetuses, buprenorphine exposed fetuses had stronger indications of fetal well-being including heart rate variability and accelerations and better coupling between fetal movements and heart rate. Similarly, Salisbury et al. (2012) found that, when compared to methadone, buprenorphine is associated with less suppression in both the fetal heart rate and biophysical profile score after medication dosing. However, the long term data about the potential effects of buprenorphine on the fetus are limited and appropriate consent is required.

If a woman in treatment is stabilized on either methadone or buprenorphine and becomes pregnant, it is reasonable to continue the same medication during pregnancy (Kaltenbach, 2012). There are some data to support the use of immediate release morphine in the transition of pregnant, methadone-stabilized women to buprenorphine but this should be done with caution under close medical supervision and only with the collaboration of a clinician experienced in addiction medicine during pregnancy (Jones et al., 2006). Medically supervised withdrawal is not recommended during pregnancy due to the high rate of relapse and potential adverse effects to the fetus of acute opioid withdrawal. It is occasionally necessary to transfer a patient from buprenorphine to methadone during the course of a pregnancy, most commonly in situations in which a patient requires more intensive, often daily, treatment and supervised medication administration. In these situations, the clinician should work closely with the staff at methadone treatment facilities.

If the decision is made to use buprenorphine during pregnancy, the patient should sign an informed consent indicating that she is aware that methadone is the standard of care during pregnancy. An example of this consent form is available in Appendix D. The patient needs to be aware that buprenorphine is not FDA approved for use during pregnancy and, if prescribed, it is considered “off label.” This consent should be included in her medical record. Many clinicians also use a separate buprenorphine contract detailing patient and provider expectations for enrollment in a buprenorphine treatment program. An example of this contract is available in Appendix E. While, in general, many treatment programs do not replace lost or stolen buprenorphine prescriptions, providers will often replace lost or stolen prescriptions in pregnant patients due to the risks to the fetus of opioid withdrawal. If the

pregnant patient loses 2 or more buprenorphine prescriptions, she may not be appropriate for an outpatient treatment program and the provider may wish to consider enrolling her in a methadone treatment program due to its daily observed medication administration.

## **Initiating treatment with buprenorphine (induction)**

Prior to initiating medication assisted treatment with buprenorphine, clinicians should confirm that the patient meets the criteria for an opioid use disorder and is pregnant. Some clinicians advocate initiating treatment only after a viable intrauterine pregnancy with a heartbeat on ultrasound has been confirmed while others will initiate treatment with a positive urine pregnancy test. It is ideal to begin treatment with buprenorphine as soon as possible after confirming an opioid use disorder and pregnancy but it is not a clinical emergency requiring immediate intervention. Ideally women will enter treatment early in pregnancy, but induction onto buprenorphine can be done at any point in the pregnancy. Some experts believe that, if a pregnant woman with an opioid use disorder is not in substance abuse treatment by 24 weeks gestation, she is probably not a good candidate for outpatient treatment with buprenorphine and should be referred to methadone (Meyer, 2012).

It is critical to know which substances are present in a woman's system prior to initiating buprenorphine treatment. A careful history should be performed and the clinician should document the risks associated with induction if certain substances are present, most importantly methadone or high dose opioids. Ideally, urine toxicology testing is performed immediately prior to induction. The medical history should include types of substances used, amounts and frequency of substances use, previous recovery attempts, and information pertaining to other medical co-morbidities as well as a detailed history of co-occurring mental health disorders. If available, the clinician should generate a report of the state's prescription monitoring program (PMP), an electronic database that collects designated data on substances dispensed in the state. A list of states with prescription monitoring programs can be found at [www.pmpalliance.org](http://www.pmpalliance.org).

Buprenorphine monotherapy (formerly known as Subutex<sup>®</sup> but now only sold in its generic form) should be used during pregnancy to prevent the possibility of acute withdrawal if the buprenorphine/naloxone combination therapy is misused or injected. The clinician should be aware that alcohol intoxication and sedative, hypnotic, or anxiolytic intoxication can create a clinical picture that resembles that of opioid intoxication, highlighting the importance of obtaining urine toxicology testing prior to initiating treatment. The anxiety and restlessness associated with opioid withdrawal can resemble the symptoms seen in sedative-hypnotic withdrawal. However, opioid withdrawal is also accompanied by rhinorrhea, lacrimation, and pupillary dilation, which are not generally seen in sedative-type withdrawal. Dilated pupils are also seen in hallucinogen intoxication and stimulant intoxication. However, other signs or symptoms of opioid withdrawal, such as nausea, vomiting, diarrhea, abdominal cramps, rhinorrhea, or lacrimation, are not present. There is limited evidence about how buprenorphine induction should occur in terms of setting (outpatient vs. inpatient) or fetal monitoring. Since induction can take many hours, some programs prefer to do inductions on an inpatient basis. However, there are no data to support that this is necessary from a safety perspective.

To effectively titrate, the patient must be in mild state of withdrawal. Most clinicians use either the Clinical Institute Narcotic Assessment (CINA) scale or the Clinical Opiate Withdrawal Scale (COWS) to assess the symptoms associated with opioid withdrawal. Examples of the CINA scale and the COWS scale are available from the Center for Substance Abuse Treatment (2004) and can be found in Appendix F and G, respectively. For the purposes of induction onto buprenorphine, mild to moderate withdrawal (e.g., CINA scores of 10 to 12) are not dangerous to the pregnancy and mild sympathetic stimulation tends to be well tolerated during pregnancy (Meyer, 2012; Vermont Department of Public Health, 2010). In addition, women with opioid use disorders who are using illicit substances are likely experiencing withdrawal on a regular basis. Because some amount of opioid withdrawal is necessary to properly assess and titrate a pregnant woman, withdrawal for the initiation of clinically appropriate treatment likely does not substantially add to this risk (Meyer, 2012).

In the Maternal Opioid Treatment Human Experimental Research (MOTHER) Trial, women were admitted to the hospital for induction onto buprenorphine (Kaltenbach, 2012). Because it was a clinical trial, all women were initially stabilized on short acting morphine prior to randomization into treatment with either methadone or buprenorphine. The initial dose of buprenorphine was based upon the amount of short acting opioids the patient had been given in the previous 24 hours. The initial dose was split with the second half of the dose administered 1 to 2 hours after the first half of the dose. During induction, CINA was administered every 6 hours and each time a comfort dose was given as needed. For the first 3 nights after induction, 2 optional comfort doses of 2 milligrams of buprenorphine were available. In the MOTHER study, women in the buprenorphine arm were more likely to discontinue treatment during the induction phase than those on methadone. It is possible that there was inadequate opioid abstinence at the time of induction which, given the partial agonist properties of buprenorphine, may have precipitated withdrawal in the pregnant women.

An alternative induction protocol involves an initial outpatient visit to gather opioid use history and discuss treatment alternatives (Meyer, 2012). The patient is then scheduled for inpatient admission for induction onto buprenorphine with an expected hospital stay of about 24 to 36 hours. The patient is instructed to abstain from using opioids in the 24 to 36 hours prior to inpatient hospitalization and is told to arrive at the hospital not feeling well. After admission, the patient is assessed with CINA scoring and is treated as scores are above 10 to 12. The initial dose is 2 milligrams and then an additional 2 milligrams is provided as CINA scores indicate. Once the patient is stabilized, she is discharged and has close follow up on an outpatient basis over the next few days. Doses are adjusted according to withdrawal symptoms and cravings during the subsequent outpatient visits.

Induction can also occur on an outpatient basis although it can be challenging to wait for patients to reach a withdrawal score that is appropriate for treatment. Outpatient induction with buprenorphine is best carried out over a 3 day period with the last 2 days sequential and early in the work week in case another office visit is necessary. The induction days are scheduled with the instruction that the patient will spend up to 8 hours at the office, should bring food with her and should not plan on driving that day.

When possible the same provider should conduct the first set of visits in order to build the patient-clinician relationship and trust. A check list of all the tasks needing completion at this first set of visits can be found in Appendix A.

Induction day begins in the morning with the patient picking up a limited supply (usually about 8 tablets) of 2 milligram buprenorphine doses from the pharmacy and bringing them to the clinic. The patient should be in mild to moderate withdrawal. After the COWS score is recorded, a urine drug screen is obtained and a pill count is conducted on the prescription that the patient brought to the clinic. The patient is then instructed to take 2 or 4 milligrams of buprenorphine depending upon her symptoms. After the dose is observed, the patient is asked to return to the waiting room with her prescription medications for 1 to 2 hours and is then seen again in the office. The COWS score is again obtained and the patient is once again observed taking another 2 to 4 milligrams of buprenorphine. A third visit is usually conducted about 2 hours later. At this point the patient has taken from 2 to 8 milligrams of buprenorphine. She is sent home with the option of taking 2 to 4 milligrams of buprenorphine as a comfort dose over the course of the evening and is then seen again the next morning.

At the visit the next day, a urine drug screen is collected as well as a pill count and COWS scoring. The final dose is then determined and a new prescription written. The patient is seen again in several days to see whether further dose adjustments are needed. A typical dose during pregnancy is 8 to 16 milligrams although some patients will require less than 8 milligrams. Although less common, patients sometimes require more than 16 milligrams daily; some insurance companies require prior authorizations to prescribe more than 16 milligrams daily.

To curb continued use of illicit substances, each woman's dose should be individually determined and not arbitrarily minimized, particularly because multiple studies show no correlation between maternal dose at delivery and the severity of NAS (Winklbaur et al., 2008; Fischer et al., 2006). The primary objective of treatment is to prevent opioid withdrawal symptoms while attenuating opioid craving and motivation to use illicit substances (Jones et al., 2008). Higher doses of buprenorphine have been associated with increased treatment retention (Fareed et al., 2012). Due to the physiological and

psychological changes of pregnancy including increased renal elimination, as many as 70% of patients will require a dose increase during the course of the pregnancy, often ranging from 3 to 6 milligrams (Jones et al., 2005; Kacinko et al., 2009; O'Connor et al., 2011; Vermont Department of Public Health, 2010).

## **Prenatal care**

Management of pregnant women with opioid use disorders usually requires a multidisciplinary approach including obstetric, pediatric, and addiction medicine specialists as well as the support of social work and other addiction counseling specialists. Because of the complex issues present when caring for this population, women should be seen frequently, often weekly, to assess progress (Young & Martin, 2012).

An ultrasound should be performed when prenatal care is initiated for the purposes of dating, particularly because last menstrual period is often unknown. A screening ultrasound is also recommended at 19 to 21 weeks to assess anatomic characteristics (Young & Martin, 2012). Due to the increased risks of intrauterine growth restriction, many experts advocate for monthly ultrasounds starting between 20 and 32 weeks (Young & Martin, 2012; The Snuggle ME Project, 2012). Doppler studies should be added as needed when intrauterine growth restriction and/or oligohydramnios is identified. It is not necessary to schedule frequent fetal testing such as non-stress tests and biophysical profiles for all patients maintained on buprenorphine and these tests should only be ordered when clinically indicated (The Snuggle ME Project, 2012).

Attention should be focused on both nausea and constipation which can be quite common in this population. Docusate sodium and polyethylene glycol can be given for constipation while promethazine and ondasteron have been used safely for nausea and vomiting. Traditional antiemetics such as ginger and pyridoxine can also be effective.

Hydroxyzine and diphenhydramine hydrochloride can be given for anxiety and restlessness (Jones et al., 2008). The use of benzodiazepines is largely contraindicated in pregnancy and the combined misuse of buprenorphine and benzodiazepines have been linked to overdose deaths (Reynaud et al., 1998).

As much as 85 to 90% of pregnant women with opioid use disorders also smoke cigarettes during pregnancy (Winklbaur et al., 2009; Maine Dartmouth internal data). The high rate of smoking as well as the possibility that heavy tobacco use is associated with a more severe neonatal abstinence syndrome suggests that the clinician should focus on education about smoking cessation (Winklbaur et al., 2009). While not specific to pregnant women, data suggest that smoking cessation among stable opioid-maintained patients does not undermine drug abstinence (Dunn et al, 2009).

Careful attention to the patient's clinical presentation as well as her ability to cope with stressors in her life may help prevent relapse. When drug use is disclosed or detected, the behavior should be acknowledged but not punished or condoned (Jones et al., 2008). If the patient is relapsing to opioids, she may require an increased dose of buprenorphine. If the patient is using substances other than opioids, it is unlikely that a dose increase will reduce this behavior as buprenorphine only treats opioid use disorders. For example, the patient may be self-medicating her anxiety with the illicit use of benzodiazepines or may be facing social pressure to use other illicit substances within her home environment. Increased emphasis on counseling including cognitive behavioral therapy might reduce the risk of further relapse.

Social factors such as homelessness, violence, poor nutrition and co-morbid psychiatric conditions can also impact pregnancy outcomes and require close attention from clinicians providing care to this highly vulnerable patient population. Inconsistent prenatal care is common among opioid-dependent pregnant women due to chaotic living situations and limited access to transportation.



## Urine toxicology

While not the standard of care for screening for substance use during pregnancy, ACOG recommends that urine drug testing can be performed as an adjunct to either detect or confirm substance use (ACOG & ASAM, 2012). Urine drug testing should only be performed with the patient's consent and providers should be sure that they are in compliance with any applicable state laws. When a patient is enrolled in substance abuse treatment, urine toxicology testing should be performed at each visit (Young & Martin, 2012). Women are often motivated to provide urine for toxicology testing as documentation of urines that contain only prescribed substances can be important evidence of the mother's recovery, especially if state law requires the notification of child protective services after delivery.

Urine toxicology can be used to both verify that a patient is taking prescribed medications and also confirm that the patient is not using any illicit or non-prescribed substances. There are a variety of potential limitations to urine drug testing including the relatively short time frame, often less than 2 to 3 days, in which substances or their metabolites are present in the urine.

Many different screening assays are available and clinicians should be aware of what is and is not included in the routine screening assay used at their hospital or practice. In some circumstances, the provider will need to order specific screening tests for substances not detected in the routine assay. For example, fentanyl and oxycodone, both highly abused medications, are often not included in standard urine drug screens. Immunoassay screening tests that are unexpectedly positive should be sent for confirmation, most often by gas chromatography–mass spectrometry (GCMS), as false positives do occur. Alternatively, the provider may choose to discuss the positive screening test with the patient before it is sent for confirmation.

Providers also need to be familiar with the expected metabolites of substances and medications commonly encountered in clinical practice and should be aware that, in some circumstances, more than one substance can be associated with any given metabolite. For example, the patient with a urine drug screen that is positive for morphine may have ingested heroin, prescription morphine, codeine (as

morphine is its primary metabolite) or poppy seeds. For this reason, patients should be counseled to avoid eating foods that contain poppy seeds while they are in treatment for an opioid use disorder.

The presence of buprenorphine in the urine can usually be detected for up to 76 hours by GCMS confirmation; norbuprenorphine, the primary metabolite, can often be detected for up to 96 hours (Kronstrand et al., 2008). The concentration of norbuprenorphine is usually greater than buprenorphine but does not have to be. Urine concentrations of buprenorphine greater than 100 nanograms per milliliter, particularly with low metabolite concentrations, are suspicious for adulteration (McMillin et al., 2012).

## **Preparing for delivery**

As the due date approaches, it is important for the clinician to review birthing plans with the patient. The clinician should document what anesthesia or analgesia was used during previous deliveries and should reassure the pregnant patient that her pain will be promptly and adequately addressed. She should be assured that the hospital, nurses and clinicians are experienced in the management of mothers on medication assisted treatment and that there is no stigma associated with her treatment with buprenorphine.

The provision of confidentiality of the mother's treatment with buprenorphine from other family members and friends who may visit should be assured. The clinician should ascertain whether the father of the baby will be involved during the delivery and, if so, discuss whether he is also in need of substance abuse treatment. Assessing the woman's safety at home is also critical. All these factors may impact any determination by state social services as to whether the infant can safely go home with his/her mother.

The extended period of hospital observation for opioid withdrawal symptoms in the newborn should be reviewed and a handout provided. The mother should be reminded that, if her infant requires treatment for NAS, hospitalization may be longer than 5 days. The clinician should encourage the patient to consider what she might like to tell her visitors about the reasons behind the extended hospital stay

particularly if her visitors do not know that she is in treatment with buprenorphine. Hospital policies regarding rooming-in, breastfeeding and smoking should be explained.

## **Intrapartum pain management**

Intrapartum pain management in women maintained on buprenorphine is often poorly understood. Current evidence suggests that the mother's buprenorphine should be continued at regular prescribed doses through labor and delivery (Alto & O'Connor, 2011; Jones et al., 2006; The Snuggle ME Project, 2012). Splitting the daily dose of buprenorphine in 4 (i.e., administering every 6 hours) may take advantage of the narcotic analgesic properties of the medication (Alford, Compton, & Samet, 2006). The buprenorphine that is prescribed to treat opioid use disorders does not provide adequate pain relief and opioid analgesics should be provided as indicated by patient symptoms. Because buprenorphine binds relatively strongly to the mu opioid receptor, higher doses than usual may be required to provide adequate pain relief (Jones et al., 2008). Regional analgesia such as an epidural may be the ideal pain management option. Commonly used medications nalbuphine (Nubain ®) and butorphanol (Stadol ®) are contraindicated as they can precipitate acute opioid withdrawal (Jones et al., 2008).

## **Postpartum management**

Following delivery, women can be continued on opioid analgesia as needed for pain (Jones, Johnson, & Milio, 2006; Jones et al., 2009). Common misperceptions should be avoided including that buprenorphine provides adequate analgesia, that the use of opioids may result in addiction relapse, that the additive effects of opioid analgesics and buprenorphine may cause respiratory and/or central nervous system depression and that the reporting of pain by women with opioid use disorder may be manipulative or drug-seeking behavior (Alford, Compton, & Samet, 2006).

NSAIDs can also be used quite effectively for pain management in the postpartum period. Women should be continued on their regular buprenorphine dose during the postpartum period and are

typically transitioned to the buprenorphine/naloxone combination therapy (Suboxone ® film or generic tablets) after delivery. Most postpartum women will require the same dose of buprenorphine as during pregnancy. If a woman's dose was increased during pregnancy, it is reasonable to consider attempting to taper the buprenorphine back to her early or pre-pregnancy dose. However, due to the postpartum risk of relapse and the increased stress of caring for a newborn, attempts to taper should not be initiated until at least 3 to 6 months postpartum. Many patients wish to be medication free postpartum but most should be counseled about the stressors associated with early motherhood as well as the increased risk of relapse during a tapering period. Women should be seen frequently, at least every 2 weeks, postpartum as they are often at risk of relapse, an exacerbation of pre-existing mental health comorbidities as well as postpartum depression.

A postpartum contraception plan should also be in place as unintended pregnancies are common among women with opioid use disorders. In a study of nearly 1,000 women with opioid use disorders, nearly 9 of every 10 pregnancies were unintended (Heil et al., 2011). The patient should be given contraception prior to discharge from the hospital as it is not uncommon for this population to miss the 6 week postpartum visit.

## **Breastfeeding and buprenorphine**

Little data are available about the effects of breastfeeding on infants born to mothers maintained on buprenorphine during pregnancy. While the buprenorphine package insert advises against breastfeeding, ACOG and ASAM (2012) agree that “patient stabilization with opioid-assisted therapy [including buprenorphine] is compatible with breastfeeding.” The concentration of buprenorphine in breast milk is similar to maternal serum levels but buprenorphine's poor oral bioavailability results in minimal infant exposure (Grimm et al., 2005; Johnson et al., 2003; Johnson et al., 2001; Lindemalm et al., 2009). The relative ingestion per kilogram of infant bodyweight is less than 1% of the dose per bodyweight of the mother (Lindemalm et al., 2009). It appears that the abrupt cessation of breastfeeding

is not associated with rebound withdrawal symptoms in infants exposed to buprenorphine in breast milk (Marquet et al., 1997). Preliminary data suggest that breastfed infants have less severe NAS (mean peak NAS 8.83 vs. 9.65 on a modified Finnegan Scoring System) and are less likely to require treatment (23.1% vs. 30%) than infants who are not breastfed (O'Connor et al., 2013) . However, further study of breastfeeding in infants exposed to buprenorphine during pregnancy is needed.

The Academy of Breastfeeding Medicine Protocol Committee (ABMPC) (2009) recommends a careful evaluation of the benefits and risks of breastfeeding in women with opioid use disorders. The committee of experts recommends breastfeeding if the woman has been engaged in substance abuse treatment and plans to continue treatment postpartum, if she has been abstinent from illicit drug use in the 90 days prior to delivery in an outpatient setting, and if she has received consistent prenatal care. The ABMPC recommends against breastfeeding in women who have not received prenatal care, have relapsed to illicit substances in the 30 days prior to delivery and who are not planning to engage in substance abuse treatment postpartum. Women who have achieved sobriety in the 30 days prior to delivery but who have relapsed in the 90 day period should be evaluated on a case by case basis. Women who have been able to maintain sobriety only in an inpatient setting and those who engaged in prenatal and/or substance abuse treatment during or after the second trimester should also be evaluated on an individual basis (ABMPC, 2009). Hospitals may have their own policies and guidelines regarding breastfeeding.

Breastfeeding is not contraindicated in infants born to mothers who have hepatitis C. Vertical transmission of the virus to the fetus is relatively low (about 5%); however, providers should be aware that the risk of transmission is higher if the mother's nipples are cracked or bleeding (Robinson, 2008). In these situations, mothers should be encouraged to pump and dispose of their breast milk until their nipples are healed. All infants born to hepatitis C positive mothers should be screened for the virus at 18 months of age (American Academy of Pediatrics, 1998). Therefore, it is important to document the mother's hepatitis status in the infant's chart.

## Neonatal abstinence syndrome

The Child Abuse Prevention and Treatment Act require states to establish procedures for the notification of substance exposed newborns to state child protective services agencies (US Department of Health and Human Services, 2009). These policies help establish a plan of care for newborns who are affected by illegal substance exposure during pregnancy or who have withdrawal symptoms associated with prenatal drug exposure. State-specific laws are often evolving and clinicians need to be aware of the applicable laws in the state(s) in which they practice.

While an extended discussion of neonatal abstinence syndrome (NAS) and its treatment is beyond the scope of this manual, clinicians should be aware that any infant exposed to buprenorphine or other opioids in utero is at risk of experiencing NAS and should be monitored appropriately. Because opioid receptors are primarily located in the central nervous system and the gastrointestinal tract, some of the more common symptoms of NAS include irritability, tremors, increased muscle tone, diarrhea and poor feeding (Hudak et al., 2012). The modified Finnegan's NAS scoring tool is one of the more common tools used in the US. It is recommended that infants should be observed for NAS in the hospital setting for 5 to 8 days after birth (Winklbaur et al., 2008). Nonpharmacologic NAS treatment modalities such as reducing environmental stimuli, swaddling and skin to skin contact are recommended. When pharmacologic therapy is indicated, the American Academy of Pediatrics recommends the use of an opioid (morphine or methadone) as first line treatment therapy (Hudak et al., 2012). Documentation of NAS should be made in the infant's chart even if the infant does not require pharmacologic treatment.

Little is known about the variables that contribute to NAS expression. Existing evidence suggests no correlation between maternal dose of buprenorphine at delivery and NAS severity (Lejeune et al., 2006). In a population of infants exposed to either methadone or buprenorphine during pregnancy, lower maternal weight, later gestation age and maternal use of selective serotonin reuptake inhibitors were associated with higher peak NAS scores (Kaltenbach et al., 2012). Male infants experience a more severe NAS and are more likely to require pharmacologic treatment than female neonates following exposure to

buprenorphine during pregnancy (O'Connor, O'Brien, & Alto, 2013). Heavy tobacco consumption has also been associated with a more severe NAS (Winklbaur et al., 2009).

Providers should be aware that exposure to other substances, including alcohol and nicotine, can effect fetal development and impact pregnancy outcomes. It is unclear whether polysubstance use has a meaningful impact on NAS outcomes. Poor placental health including chronic hypoxia of the chorial disc and retroplacental hematomas which can be seen in pregnancies complicated by substance abuse is associated with a prolonged and more severe withdrawal syndrome (Domenici et al., 2009).

Some experts advocate meconium toxicology testing to identify illicit substance use during pregnancy. While meconium screens can be useful, particularly in situations in which little is known about potential exposure during pregnancy (e.g., little or no access to prenatal care or late identification of a substance use disorder), the clinician should be aware of the potential shortcomings of meconium screening. Because meconium is difficult to collect, store and analyze, meconium results are often negative even with established illicit substance use (Arendt et al., 1999). According to the American Academy of Pediatrics, “the use of meconium to determine the timing or extent of exposure during pregnancy is controversial because of a lack of studies regarding the effects of the timing and quantity of the postpartum specimen collection as well as the effects of urine or transitional stool contamination of the meconium samples.” (Behnke et al., 2013). Rather than meconium testing, a clinician may choose to send the infant’s first urine for toxicology testing. However, if the mother provided a urine for toxicology testing upon admission to labor and delivery, screening the infant’s urine is likely redundant. In addition, if the infant’s urine is sent for toxicology testing, the clinician needs to be aware that any opioid analgesics administered to the mother during labor and delivery may be present in the infant’s urine.

The infant’s parents should be reassured frequently about what to expect during scoring for NAS and when treatment may be initiated. The mother’s mental health should also be carefully assessed as it is not uncommon for women to feel guilty about their infant’s withdrawal symptoms. Parents can be encouraged to provide supportive care to their infants by:

- Keeping the infant’s surroundings quiet and calm and the lights low.

- Using a soft voice when speaking to the infant.
- Caring for the infant without “handling” him or her too much.
- Touching and moving the infant gently and slowly.
- Cuddling the infant skin-to-skin and swaddling the infant when he/she is not skin-to-skin.

## **Long term implications of exposure to buprenorphine during pregnancy**

Little is known about potential long term developmental outcomes following exposure to buprenorphine during pregnancy. It is difficult to determine the potential effects of buprenorphine particularly when maternal polysubstance use is present. Lifestyle factors that often occur in tandem with substance use disorders such as homelessness, little prenatal care, and poor nutrition are also likely to impact long term developmental outcomes. Sarfi et al. (2009) found no differences in sleep patterns, wakefulness and distress when comparing 3 month old infants exposed to either buprenorphine or methadone during pregnancy to a group of unexposed infants. Similarly, Whitham et al. (2010) found no significant differences in neurologic development as measured by visual evoked potentials when comparing a group of infants exposed prenatally to buprenorphine to a non-exposed control group. In contrast, Whitham et al. (2010) found that infants exposed prenatally to methadone had a significantly prolonged response to smaller stimuli (which require more maturation of the visual system) when compared to those exposed to buprenorphine during pregnancy.

Coyle et al. (2012) also found that, when compared to exposure to methadone during pregnancy, buprenorphine exposure is associated with superior neurobehavioral scores during the first month of life. This suggests that the use of buprenorphine during pregnancy may confer additional advantages beyond the period when NAS may occur. An internal Maine Dartmouth analysis of 46 infants exposed to buprenorphine during pregnancy as compared to 46 infants born to mothers not enrolled in medication assisted treatment or using illicit substances during pregnancy found no differences in weight, height or head circumference at one year of age after controlling for poverty, gender and gestational age at delivery.



In addition, there were no differences in 13 developmental milestones including gross and fine motor skills and verbal development as well as no significant differences in the frequency of chronic medical illnesses between the exposed and unexposed populations.

## **Appendix A. Management of pregnant women with opioid use disorders using buprenorphine checklist**

### First visit

Pregnancy test

Urine drug screen (UDS)

Patient sign release to obtain previous records

Run prescription monitoring program (PMP) report

Dating ultrasound

Routine prenatal labs

Hepatitis C antibody

Consider additional infectious disease screening (e.g., tuberculin skin test and/or chlamydia and gonorrhea testing onto first urine)

Assess need for bowel regimen and anti-emetics

Sign consent for use of buprenorphine during pregnancy

Sign standard buprenorphine contract

Complete prior authorization if required by patient's insurance

Connect patient with social worker (ideally warm hand off)

Initial note documents discussion of neonatal abstinence syndrome (NAS), mandated reporting to child protective agencies based on state specific law, discussion of methadone being the standard of care, mandatory counseling requirement, patient's addiction history and evidence that the patient meets the criteria for an opioid use disorder.

Patient scheduled to be seen at least weekly until in the program for 8 weeks

Refer patient to substance abuse counseling and have patient sign consent to communicate with substance abuse providers.

### Routine prenatal care in addition to

UDS obtained at every visit to office

Confirm attendance in substance abuse counseling

Monitor for signs and symptoms of opioid withdrawal/craving at every visit

Documented conversation about NAS in third trimester

Documented conversation about mandated referral to child protective agencies in third trimester based on state specific law

Documented conversation about pain management during delivery/post-partum

Growth ultrasound (US) at 20-32 weeks and, if any concern, schedule for monthly US and dopplers

Repeat Hepatitis C/HIV/other infectious disease testing in the third trimester if patient at risk or there is a delay between exposure and development of disease

Discuss breastfeeding implications as appropriate

### After delivery

Follow up visit for the mother less than 1 week after delivery

Switch to buprenorphine/naloxone combination therapy at first postpartum medication refill

Documentation of neonatal abstinence syndrome in infant chart regardless of scoring or whether medications were required for the treatment of NAS

Review mother's Hepatitis C status – update infant's chart so that infant can be screened at 18 months of age as indicated

Contraception plan in place before mother leaves hospital

Close attention to mother's mental health

## **Appendix B. 4 P's**

**Parents:** Did any of your parents have a problem with alcohol or other drug use?

**Partner:** Does your partner have a problem with alcohol or drug use?

**Past:** In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?

**Present:** In the past month have you drunk any alcohol or used other drugs?

**Scoring:** Any "yes" should trigger further questions.

*Source: American College of Obstetricians and Gynecologists, & American Society of Addiction Medicine (2012). Opioid abuse, dependence, and addiction during pregnancy. Committee Opinion No. 524, May 2012.*

## **Appendix C. CRAFFT – Substance abuse screen for adolescents and young adults**

**C** Have you ever ridden in a CAR driven by someone (including yourself) who was high or had been using alcohol or drugs?

**R** Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?

**A** Do you ever use alcohol or drugs while you are by yourself or ALONE?

**F** Do you ever FORGET things you did while using alcohol or drugs?

**F** Do your FAMILY or friends ever tell you that you should cut down on your drinking or drug use?

**T** Have you ever gotten in TROUBLE while you were using alcohol or drugs?

Scoring: Two or more positive items indicate the need for further assessment.

*Source: American College of Obstetricians and Gynecologists, & American Society of Addiction Medicine (2012). Opioid abuse, dependence, and addiction during pregnancy. Committee Opinion No. 524, May 2012.*

## Appendix D. Consent for treatment with buprenorphine during pregnancy

Patient's printed name: \_\_\_\_\_

I give consent to Dr. \_\_\_\_\_ to treat me with buprenorphine during my pregnancy.

My doctor (named above) has explained the following about the proposed treatment:

- What it involves;
- The benefits, risks or side effects, including any problems that may occur;
- The likelihood of achieving treatment goals;
- Other treatment choices and their risks, benefits and side effects.

\_\_\_\_\_ I have been diagnosed with an opioid use disorder and understand that it is safer to treat this disorder during pregnancy than to continue using other opioids or abruptly stop using opioids and experience withdrawal.

\_\_\_\_\_ I understand that if I continue to get high during pregnancy or experience withdrawal, my baby might experience a number of complications including being born too early, having trouble growing in my uterus and might die.

\_\_\_\_\_ I understand that methadone continues to be the standard of care for the treatment of opioid use disorders during pregnancy. Methadone has been available for more than 40 years so more is known about the short and long term impacts of using this medication during pregnancy. Buprenorphine is a newer medication. While preliminary evidence suggests that it is as safe as methadone for me and my baby, no long term studies are currently available. I understand that it is possible that the use of buprenorphine during pregnancy may have lasting effects on my baby as he/she grows.

\_\_\_\_\_ I understand that a problem with taking any opioid during pregnancy (including methadone or buprenorphine) is that my baby may have a withdrawal syndrome called Neonatal Abstinence Syndrome after birth. Babies with Neonatal Abstinence Syndrome may experience trouble

sleeping or feeding, tremors, sneezing, irritability, vomiting, weight loss, and seizures. Neonatal Abstinence Syndrome can be safely treated with medications and/or other therapies.

\_\_\_\_\_ I understand that my baby will be monitored for Neonatal Abstinence Syndrome in the hospital for at least 5 days after birth, and may require treatment. If treatment is required, the hospitalization period may be much longer.

\_\_\_\_\_ I understand that, if I use medications or other substances not prescribed to me such as benzodiazepines, amphetamines, cocaine, or marijuana during pregnancy, it may affect the health of my baby. I also understand that buprenorphine does not treat dependence on, or addiction to, any of these other substances.

I have discussed the benefits and risks of the use of buprenorphine during pregnancy and I have decided to take buprenorphine rather than methadone. I understand that medical knowledge on the actual or potential risks of buprenorphine on pregnant women and unborn children is still uncertain.

My doctor has explained this treatment to me and answered all of my questions to my satisfaction.

I know I can change my mind and can withdraw this consent.

\_\_\_\_\_  
Patient Name (print)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Patient Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Provider Signature

\_\_\_\_\_  
Date

## Appendix E. Standard contract for treatment with buprenorphine

Patient Name: \_\_\_\_\_

DOB: \_\_\_\_\_

- I understand that I have been diagnosed with an opioid use disorder. I have elected to enter [practice name] outpatient buprenorphine treatment program.
- I understand that buprenorphine is a narcotic medication and that buprenorphine, like all narcotics, may make me drowsy. If I have this side effect, I should not drive, operate equipment, or perform any duty or task that requires complete mental or physical alertness.
- I understand that not everyone is appropriate for treatment with buprenorphine. If, at any point within treatment, my provider thinks that methadone is a more appropriate treatment option for me, I will be referred to a methadone clinic. In these cases, I understand that [PRACTICE NAME] is not obligated to provide any further buprenorphine prescriptions and that [PRACTICE NAME] has no control over the availability of treatment at methadone clinics.
- I agree to take my buprenorphine only as prescribed. I will not increase my dose or frequency of use under any circumstances. The only person who can adjust my buprenorphine dose is my provider. If I take more buprenorphine than I am prescribed, I understand that my prescription will not be refilled early and may not be refilled at all.
- I understand that any lost, misplaced, or stolen buprenorphine prescriptions or medication will not be replaced or refilled early even if I have a police report.
- I understand that I need to meet regularly with my provider to assess my progress. Depending upon my individual needs, these visits may be up to daily. I understand that, even if I am stable in recovery, I need to schedule an office visit at least once a month. It is my responsibility to schedule these appointments.
- I understand that my buprenorphine may not be refilled if I am not able to attend my appointments as scheduled.
- I understand that frequent cancellations and/or no shows for office visits will be considered a violation of this contract.
- I will abstain from the use of medications and/or substances not prescribed to me (both legal and illegal) during my treatment. I will also abstain from alcohol, and other sedatives, anxiolytics, or tranquilizers, which may have an addictive effect, as well as possession of any and all paraphernalia.



- I understand that the misuse of buprenorphine on its own or in combination with other substances particularly benzodiazepines and alcohol may result in drug overdose and/or death.
- I understand that it is my responsibility to be sure that [PRACTICE NAME] can reach me. I understand that [PRACTICE NAME] must have at least two ways to contact me by phone including by voicemail. I must return voicemail messages within 24 hours. If my phone numbers change, I must notify [PRACTICE NAME] within 24 hours.
- If I use more than one last name (i.e., a maiden and married name), I will provide a list of these names to [PRACTICE NAME].
- I understand that if prescriptions for narcotics and/or other controlled substances are needed, these medications should only be prescribed by [PRACTICE NAME]. If I am in treatment with another specialist, I will notify [PRACTICE NAME] of any new medications or changes to my current medication regimen within 48 hours.
- If I need to seek emergency care and I think that I have been prescribed, and/or provided with, a narcotic medication or other controlled substance, I must notify [PRACTICE NAME] within 24 hours.
- I understand that substance abuse counseling is a mandatory component of [PRACTICE NAME]'s buprenorphine treatment program. My provider will help me identify the best counseling option. I understand that the frequency and/or type of counseling may depend upon my recovery progress. My provider may require me to attend more intensive treatment at any time. I understand that failure to comply with these recommendations is grounds for dismissal.
- I understand that I must sign a release for [PRACTICE NAME] to speak with my substance abuse counselor.
- I understand that I am expected to keep a record of my substance abuse counseling and that I need to present this to my provider at every office visit.
- I understand that, if I do not complete my counseling requirements, I will likely no longer be able to receive care at [PRACTICE NAME]'s buprenorphine treatment program.
- I understand that I am expected to leave a urine drug screen at every visit. I will only supply my own urine and I agree not to tamper with my urine in any way. If I am unable to leave a urine sample, I understand that I may be asked to leave a catheterized and/or blood specimen prior to receiving my medication.

- I understand that the collection of my urine drug screen may be observed by a member of the [PRACTICE NAME] clinical staff at any time.
- I agree to random urine and/or blood tests to assess my compliance with my prescribed medications, including buprenorphine
- I also agree to random requests for medication verification through pill/film counts.
- I understand that I will be asked to present for a random urine drug screen and/or pill/film count within 24 hours. I understand that failure to comply with this request will be considered a violation of this contract.
- I understand that if my provider determines that the medication has lost its effectiveness in increasing my function, I will be promptly tapered off the medication.
- I understand the eventual goal is to taper my buprenorphine while in outpatient treatment.
- I understand that I must behave appropriately at all times. Abusive and/or threatening behavior, physical or verbal, will not be tolerated and are grounds for immediate dismissal. Illegal activities including, but not limited to, prescription alterations and/or selling prescribed medications are also grounds for immediate dismissal. I understand that [PRACTICE NAME] will also notify the appropriate authorities as indicated.
- I understand and agree to the release of all information regarding my use or misuse of medication, whether legal or illegal, by [PRACTICE NAME] to any pharmacy, other physician, or medical treatment facility to which my provider deems medically necessary.
- I understand that, like all health care providers, [PRACTICE NAME]'s providers are mandated reporters of suspected abuse, neglect or exploitation of certain groups of people including children. Most states have a specific law mandating the referral of all drug affected infants to child protective agencies.
- I understand that it is not the responsibility of [PRACTICE NAME] to supply any of my medications, and I am solely responsible for them.
- I understand that buprenorphine is pregnancy category C. It is my responsibility to notify my provider if I think I might be pregnant, if I am trying to get pregnant or if I am not always using contraception when I am sexually active. Under these circumstances, buprenorphine may or may not be the right medication for me.

- I am aware that failure to comply with any of the rules in this contract is grounds for my dismissal from the program without further medications or a rapid taper off of the medication (at a rate at or above 25% per day).

I have read, understand, and have been afforded answers to any and all questions that I have asked. By signing this contract, I agree to all the conditions of this contract.

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Patient Name (print)

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Date

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Patient Signature

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Date

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Provider Signature

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Date

## Appendix F. Clinical institute narcotic assessment (CINA) scale

The Clinical Institute Narcotic Assessment (CINA) Scale measures 11 signs and symptoms commonly seen in patients during narcotic withdrawal. This can help to gauge the severity of the symptoms and to monitor changes in the clinical status over time.

PARAMETERS	FINDINGS	POINTS
<i>Parameters based on Questions and Observation:</i>		
<b>(1) Abdominal changes:</b> Do you have any pains in your abdomen?	• No abdominal complaints; normal bowel sounds	0
	• Reports waves of crampy abdominal pain	1
	• Crampy abdominal; diarrhea; active bowel sounds	2
<b>(2) Changes in temperature:</b> Do you feel hot or cold?	• None reported	0
	• Reports feeling cold; hands cold and clammy to touch	1
	• Uncontrolled shivering	2
<b>(3) Nausea and vomiting:</b> Do you feel sick in your stomach? Have you vomited?	• No nausea or vomiting	0
	• Mild nausea: no retching or vomiting	2
	• Intermittent nausea with dry heaves	4
	• Constant nausea; frequent dry heaves and/or vomiting	6
<b>(4) Muscle aches:</b> Do you have any muscle cramps?	• No muscle aching reported; arm and neck muscles soft at rest	0
	• Mild muscle pains	1
	• Reports severe muscle pains; muscles in legs arms or neck in constant state of contraction	3
<i>Parameters based on Observation Alone:</i>		
<b>(5) Goose flesh skin</b>	• None visible	0
	• Occasional goose flesh but not elicited by touch; not permanent	1
	• Prominent goose flesh in waves and elicited by touch	2
	• Constant goose flesh over face and arms	3
<b>(6) Nasal congestion</b>	• No nasal congestion or sniffing	0
	• Frequent sniffing	1
	• Constant sniffing watery discharge	2

<b>(7) Restlessness</b>	<ul style="list-style-type: none"> <li>• Normal activity</li> <li>• Somewhat more than normal activity; moves legs up and down; shifts position occasionally</li> <li>• Moderately fidgety and restless; shifting position frequently</li> <li>• Gross movement most of the time or constantly thrashes about</li> </ul>	0 1 2 3
<b>(8) Tremor</b>	<ul style="list-style-type: none"> <li>• None</li> <li>• Not visible but can be felt fingertip to fingertip</li> <li>• Moderate with patient's arm extended</li> <li>• Severe even if arms not extended</li> </ul>	0 1 2 3
<b>(9) Lacrimation</b>	<ul style="list-style-type: none"> <li>• None</li> <li>• Eyes watering: tears at corners of eyes</li> <li>• Profuse tearing from eyes over face</li> </ul>	0 1 2
<b>(10) Sweating</b>	<ul style="list-style-type: none"> <li>• No sweat visible</li> <li>• Barely perceptible sweating: palms moist</li> <li>• Beads of sweat obvious on forehead</li> <li>• Drenching sweats over face and chest</li> </ul>	0 1 2 3
<b>(11) Yawning</b>	<ul style="list-style-type: none"> <li>• None</li> <li>• Frequent yawning</li> <li>• Constant uncontrolled yawning</li> </ul>	0 1 2
<b><i>TOTAL SCORE</i></b>	Minimum score: 0 Maximum score: 31. The higher the score, the more severe the withdrawal syndrome.	<i>Sum of points for all 11 parameters</i>

Source: Adapted from Peachey J. E., and Lei H. Assessment of opioid dependence with naloxone. *British Journal of Addiction* 83(2): 193-201, 1988.

## Appendix G. Clinical opiate withdrawal scale (COWS)

For each item, circle the number that best describes the patient's signs or symptoms. Ratings should be based only on the signs and symptoms related to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

<b>Reason for this assessment:</b>	
<b>1. Resting pulse rate:</b> ____beats/minute Measured after the patient is sitting or lying for one minute. 0 Pulse rate 80 or below 1 Pulse rate 81-100 2 Pulse rate 101-120 4 Pulse rate greater than 120	<b>7. GI upset:</b> over last half hour 0 No GI symptoms 1 Stomach cramps 2 Nausea or loose stool 3 Vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
<b>2. Sweating:</b> over past half hour not accounted for by room temperature or patient activity 0 No reports of chills or flushing 1 Subjective reports of chills or flushing 2 Flushed or observable moisture on face 3 Beads of sweat on brow or face 4 Sweat streaming off face	<b>8. Tremor:</b> observation of outstretched hands 0 No tremor 1 Tremor can be felt, but not observed 2 Slight tremor observable 4 Gross tremor or muscle twitching
<b>3. Restlessness:</b> observation during assessment 0 Able to sit still 1 Reports difficulty sitting still, but is able to do so 3 Frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	<b>9. Yawning:</b> observation during assessment 0 No yawning 1 Yawning once or twice during assessment 2 Yawning three or more times during assessment 4 Yawning several times/minute
<b>4. Pupil size</b> 0 Pupils pinned or normal size for room light 1 Pupils possibly larger than normal for room light 2 Pupils moderately dilated 5 Pupils so dilated that only the rim of the iris is visible	<b>10. Anxiety or irritability</b> 0 None 1 Patient reports increasing irritability or anxiousness 2 Patient obviously irritable, anxious 4 Patient so irritable or anxious that participation in the assessment is difficult

<p><b>5. Bone or joint aches:</b> if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored.</p> <p>0 Not present</p> <p>1 Mild diffuse discomfort</p> <p>2 Patient reports severe diffuse aching of joints/muscles</p> <p>4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>	<p><b>11. Gooseflesh skin</b></p> <p>0 Skin is smooth</p> <p>3 Piloerection of skin can be felt or hairs standing up on arms</p> <p>5 Prominent piloerection</p>
<p><b>6. Runny nose or tearing:</b> not accounted for by cold symptoms or allergies</p> <p>0 Not present</p> <p>1 Nasal stuffiness or unusually moist eyes</p> <p>2 Nose running or tearing</p> <p>4 Nose constantly running or tears streaming down cheeks</p>	<ul style="list-style-type: none"> <li>• Total Score: _____ (The total score is the sum of all 11 items.)</li> <li>• Initials of person completing assessment: _____</li> </ul>
<p><i>Score: 5-12 Mild; 13-24 Moderate; 25-36 Moderately severe; &gt;36 Severe withdrawal</i></p>	

*Source: Wesson DR, Ling W, Jara G. Buprenorphine in Pharmacotherapy of Opioid Addiction: Implementation in Office-Based Medical Practice. In: Committee on Treatment of Opioid Dependence, editor. Translating the Experience of Clinical Trials into Clinical Practice. California Society of Addiction Medicine; San Francisco, CA: 1999.*

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