# Methadone and buprenorphine pharmacotherapy of opioid use disorder during pregnancy

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## INTRODUCTION

Methadone and buprenorphine are used for pharmacotherapy of opioid use disorder (OUD) and medically assisted withdrawal, along with appropriate social and medical services. The advantages and disadvantages of methadone versus buprenorphine pharmacotherapy of OUD are compared in the table (table 1) and discussed in more detail elsewhere. (See "Overview of management of opioid use disorder during pregnancy", section on 'Methadone or buprenorphine pharmacotherapy?'.)

This topic will discuss administration and outcomes of methadone and buprenorphine for pharmacotherapy of OUD during pregnancy and postpartum. The use of pharmacotherapy versus medically-assisted withdrawal, choice of drug for pharmacotherapy, candidates for this therapy, maternal and fetal evaluation, labor and delivery management, and postpartum pain control are reviewed separately. (See "Overview of management of opioid use disorder during pregnancy".)

## METHADONE PHARMACOTHERAPY

**Provider** — Regulations regarding provision of methadone for OUD vary by state and/or country [1]. The provider should be aware of all opioid prescribing laws applicable in his/her area.

Successful pharmacotherapy of OUD depends upon a comprehensive, multidisciplinary, coordinated approach to care [2,3]. Methadone treatment centers usually offer individual and group

counseling, and some but not all may provide psychiatric and social services. A few, unique programs also offer health/parenting education and prenatal care.

**Pharmacology** — Methadone is a synthetic long-acting opioid agonist that binds to and occupies mu-opioid receptors, which prevents withdrawal symptoms for 24 hours or longer, reduces craving for opioids, and, by maintaining high levels of opioid tolerance, reduces the euphoric effects of subsequent nonprescription opioid use.

It is available as an oral solution, tablet, and injectable solution. The oral solution is used for observed ingestion; the oral solution or tablets are used for take-home doses [4]. The injectable solution is not used for pharmacotherapy of OUD.

The half-life of methadone falls substantially during pregnancy, from an average of 22 to 24 hours in nonpregnant women to 8.1 hours in pregnant women, due to changes in pharmacokinetics related to pregnancy [5,6]. Methadone metabolism is consistently accelerated in pregnancy due to significantly increased CYP3A4 expression by a variety of organs, including liver, intestine, and placenta [5,7,8]. Significant genetic diversity in the enzymes that metabolize methadone (CYP3A4, 2D6) result in different individual metabolic rates, and absorption is variable in pregnant women [9]. Metabolism generally increases with advancing gestational age [10-15]; therefore, higher doses or split dosing may be required to maintain therapeutic effects as pregnancy progresses.

Cord blood methadone levels correlate with maternal dose and gestational age as methadone crosses the placenta in greater amounts in late pregnancy [12].

### Initial dosing

- **When to start** – For pregnant women desiring methadone pharmacotherapy, the drug should be initiated as early in gestation as possible to get the most benefit. Some, but not all, studies have shown an improvement in perinatal outcome with earlier initiation of methadone (eg, longer gestation, greater birth weight) [16-19], but regardless of whether or not this is true, treatment should not be delayed since there are other benefits, such as the reduction in overdose.

  If the diagnosis of OUD is clear (table 2), there is no requirement that the patient demonstrate signs and symptoms of withdrawal before initiating methadone. Signs and symptoms of opioid withdrawal typically appear four to six hours after the last dose of short-acting opioids, peak at one to three days (onset of and peak symptoms may occur later after long-acting opioids) [20], and include one or more of the signs/symptoms in the table (table 3). The severity of each symptom depends on the individual's tolerance to opioids, the continued presence of opioid in the serum and end organs, and the duration of time over which withdrawal has occurred.

Withdrawal symptoms generally subside after five to seven days [21]. (See "Opioid withdrawal in the emergency setting", section on 'Clinical features of opioid withdrawal'.)

- **Where to start** – The optimum setting for initiation of therapy has not been evaluated in the pregnant population. We suggest hospitalization during initiation of treatment because of the potential for serious adverse events, such as overdose and adverse drug interactions. It also facilitates daily fetal assessment (fetal heart rate or nonstress test depending on gestational age), which we perform in inpatients until the patient is stabilized (ie, when methadone occupies a sufficient number of opioid receptors to prevent withdrawal). This is also an ideal time for assessment by a social worker and case manager and for initiation of prenatal care. However, some authorities believe hospitalization is not necessary at initiation of therapy.

  It is important to emphasize that the approach described below applies to women who are hospitalized while initiating methadone; initiation and titration of methadone in the outpatient setting must be guided by a different protocol. The dose adjustment recommended below should only be done in the inpatient setting as the upward titration described is too rapid to be safe for all patients in an outpatient setting where the dose is typically increased no more frequently than every three to five days. Detailed information on dosing in the outpatient setting is available separately. (See "Pharmacotherapy for opioid use disorder".)

**Starting dose in hospitalized women** — In most symptomatic women, we begin therapy with a single oral dose of methadone 20 to 30 mg [10,22-26]. After this dose, incremental doses of 5 to 10 mg are provided every three to six hours as needed to treat withdrawal symptoms (table 3) [22]. United States Federal Regulations limit the initial dose to a maximum of 30 mg and the total first day dose to a maximum of 50 mg if withdrawal symptoms are not fully suppressed by the initial dose.

For women with no or only mild symptoms of withdrawal, an alternative approach is to begin with a low initial dose of methadone 10 mg and provide incremental doses of 5 to 10 mg every four to six hours as needed for withdrawal symptoms on the first day of therapy. Mild symptoms of withdrawal can sometimes be managed adequately with counseling, supportive care, and/or clonidine 0.1 mg orally every four to six hours rather than with incremental doses of methadone.

Clinical observation and a structured instrument with a standardized scoring system (eg, Clinical Opiate Withdrawal Scale (table 4)) can be used to assess the progress and severity of withdrawal. (See "Medically supervised opioid withdrawal during treatment for addiction", section on 'Monitoring'.)

**Dose adjustments in hospitalized women after the first day of treatment** — On the second

day of hospital treatment, the total dose of methadone administered over the previous 24 hours is provided as the new morning dose. Women who initially presented with no or only mild symptoms and were given a low initial dose (10 mg) are provided no less than 30 mg on the second day. Incremental doses are provided as needed.

Daily increments to the morning dose are made until no additional incremental doses are needed to prevent signs and symptoms of withdrawal for at least 24 hours. This is the "stabilization dose" and is achieved when methadone occupies enough opioid receptors to prevent withdrawal [27]. Stabilization may take a week or more, and further adjustments over time may be needed. (See 'Maintenance dosing after hospital discharge' below.)

**Maintenance dosing after hospital discharge** — Once the initial stabilization dose has been achieved, we discharge the patient, and further adjustments are made at an outpatient treatment center. The dose is not increased for several days even if symptoms occur; we usually wait at least 72 hours before considering an increase in dose [28]. Common discomforts of pregnancy such as nausea, vomiting, and low back pain are similar to some opioid withdrawal symptoms; this possibility should be taken into account before increasing the daily methadone dose in symptomatic women [29].

After this 72-hour period, we increase the methadone dose in 5 to 10 mg increments per week, when indicated based on clinical evaluation, to maintain the lowest dose that controls withdrawal symptoms and minimizes cravings. The average woman will require three medication dose increases during the course of pregnancy because of increased metabolism related to the pregnant state [30]. (See 'Pharmacology' above.)

In our experience, the average dose is approximately 120 mg per day. The optimal dose in pregnancy is controversial. Research from the National Institute on Drug Abuse indicates that methadone doses less than 60 mg are ineffective since they are less likely to prevent drug-seeking behavior. Pregnant women appear to do better on higher (80 to 120 mg/day) rather than lower methadone doses [31]; doses at these levels are not overly sedating because tolerance develops [28]. The rationale for high-dose therapy is to reach a level sufficiently high that additional doses of nonprescription opioids do not result in euphoria [24,28].

**Split dosing** — Twice-daily dosing at 12-hour intervals (or rarely, three times daily at 8-hour intervals) results in more sustained plasma levels, fewer withdrawal symptoms, and less nonprescription opioid use than a single high methadone dose [6,32]. Another advantage of split dosing is that it does not suppress fetal movement and breathing as much as single dosing [33,34].

However, split dosing is not possible for all women because it requires take-home doses. Federal and state regulations list criteria for patients who may have doses of methadone to take home. Eligibility for take-home doses is usually based on adherence to program requirements for counseling and abstinence from nonprescription opioids and other prescription medication misuse (based on urine toxicology testing), as well as absence of recent criminal activity and capacity to store the take-home doses safely in the home environment.

**Missed dose** — If a woman misses a methadone dose, and this is confirmed with the opioid treatment program, she can resume therapy at the same dose if she has not missed more than three daily doses; after three days of missed doses, she would need restabilization.

If the missed dose cannot be confirmed, methadone should not be provided. The patient should be admitted and assessed for withdrawal using the Clinical Opiate Withdrawal Scale [35]. If she is demonstrating signs or symptoms of withdrawal, methadone can be provided in incremental doses up to 50 percent of the reported maintenance dose until additional management can be coordinated with her opioid treatment program.

There is no specific requirement for fetal monitoring due to a missed dose in the absence of standard obstetric indications for fetal surveillance, though some centers routinely obtain a nonstress test or biophysical profile on all women presenting to the labor and delivery triage unit with pregnancies at or beyond viability.

**Urine drug testing** — After the initial urine drug screening test (UDS) on initiation of care, serial UDS are performed to monitor for continued nonprescription opioid use. Ideally, UDS is performed at weekly visits; in the United States, federal regulations require UDS with a minimum of eight urine tests per year of treatment [36]. UDS is also recommended on admission to the hospital whether for delivery or other reasons (especially complications possibly associated with nonprescription opioid use [eg, abruption]). A single positive UDS rarely would lead to discontinuation of medication-assisted treatment. The American Society of Addiction Medicine provides guidelines on the appropriate use of drug testing [37]. Their recommendations are available in multiple forms including an online pocket guide and mobile app [38].

One- to two-thirds of women enrolled in methadone programs continue to use nonprescription opioids and/or misuse other prescription medications or alcohol during pregnancy [39]. Detection of continued polysubstance use is important because it is an indication for additional psychosocial intervention and possibly an increase in methadone dose. In addition, continued polysubstance use may lessen some of the benefits of methadone therapy and increase the incidence and severity of neonatal abstinence syndrome (NAS) [17,40]. Benzodiazepines, in particular, have been associated with lower birth weight and increased incidence and severity of NAS when used

concomitantly with methadone [25,41,42]. Additionally, co-prescribing methadone (or buprenorphine) with benzodiazepines may increase the risk of maternal respiratory difficulties, coma, or death; carefully tapering benzodiazepines is recommended.

UDS vary with respect to the drugs included in the testing panel. Most panels include naturally occurring opioids and their metabolites, methadone, cocaine, benzodiazepines, barbiturates, amphetamines, and phencyclidine. Testing for synthetic opioids (eg, oxycodone, fentanyl, meperidine, hydromorphone) and buprenorphine may need to be ordered separately. However, an increasing number of commercially available panels test for more substances, including some synthetic opioids (eg, oxycodone, buprenorphine). Providers should be aware of the specific drug tests available to them locally. A detailed discussion of urine drug screening and testing, including interpretation, limitations, validity, and reliability, can be found elsewhere. (See "Testing for drugs of abuse (DOA)".)

**When to check methadone levels** — There is no defined therapeutic window, but a methadone trough level of 300 to 400 ng/mL in nonpregnant individuals suggests an adequate total methadone dose and reduced likelihood of heroin use [43]. This is consistent with observations in pregnant women. In a prospective study that evaluated serum trough levels in a cohort of pregnant women, asymptomatic women had mean trough levels of 300±160 ng/mL, which was significantly higher than mean trough levels in symptomatic women (180±110 ng/mL) [44].

Methadone levels are unnecessary in asymptomatic women. Determination of a therapeutic dose is based on patient response, which can vary widely among patients [45]. A single methadone trough level can be difficult to interpret. We recommend checking a methadone serum trough level in women who remain symptomatic despite increases in methadone dose and in women who are excessively sedated two to four hours after dose administration but develop craving or withdrawal symptoms before the next dose is due. Trough levels should be drawn 24 hours after methadone dose administration [45].

Symptoms in women with a peak to trough ratio >2:1 may indicate rapid metabolism [46]. These women may benefit from split dosing. (See 'Split dosing' above.)

If the trough level is low, management should be guided by symptoms. Withdrawal symptoms in women with a low trough level suggest that an increased dose, rather than split dosing, may be needed. Excessive sedation with a low trough level often indicates ongoing nonprescription opioid use. However, the turnaround time for the test is typically >7 days, which makes it somewhat impractical.

Note: Drug levels are not useful during induction of methadone because a steady state has not

been achieved yet.

**Side effects** — Side effects of chronic methadone therapy include constipation, mild drowsiness, excessive sweating, and peripheral edema. Chronic use of methadone and other opioid agonists may result in an increased sensitivity to pain, which may develop within a month of initiating chronic opioid therapy. (See "Pharmacotherapy for opioid use disorder", section on 'Adverse effects'.)

Methadone can prolong the QT interval and cause torsades de pointes and sudden death. Higher methadone doses increase the risk for these events [47].

The confounding influence of other drugs (eg, azithromycin, erythromycin, metronidazole, mifepristone, ondansetron, promethazine, and selective serotonin reuptake inhibitors), a prolonged QT interval at baseline, and hypokalemia also contribute to this risk. An electrocardiogram is recommended before initiation of methadone for patients with significant risk factors [45].

This complication of methadone therapy and approaches to identify patients at high arrhythmic risk are discussed in detail elsewhere. (See "Pharmacotherapy for opioid use disorder", section on 'Adverse effects'.)

**Drug interactions** — Clinicians should be aware that drug-drug interactions may occur with several common medications and may require the patient's daily methadone dose to be adjusted to prevent complications from such drug-drug interactions. A number of the drug interactions are based on metabolism by the cytochrome P450 isoenzyme system, specifically 3A4. Selected interactions are discussed below and more information is available in the Lexicomp drug interactions program.

- Magnesium sulfate – Though there may be a theoretical risk of additive central nervous system and/or cardiorespiratory depressive effects with combined use of opioids and high doses of magnesium sulfate (as used for prevention of eclamptic seizures or for fetal/neonatal neuroprotection), we have neither observed nor read case reports of such adverse drug interactions and do not alter dosing in patients receiving both drugs during labor.

- **Opioid antagonists** – Naloxone and other narcotic antagonists may precipitate withdrawal in both the mother and fetus [5,10,48]. Mixed agonists/antagonist analgesics that are sometimes considered for labor analgesia (eg, nalbuphine, butorphanol, pentazocine) should be avoided. (See "Acute opioid intoxication in adults", section on 'Basic measures and antidotal therapy' and "Prevention of lethal opioid overdose in the community".)

- Rifampin – The antituberculosis drug rifampin induces CYP3A4 and alters P-glycoprotein

binding [48,49], which reduces the plasma concentrations of methadone and may lead to opioid withdrawal. Therefore, higher doses of methadone may be required in pregnant women who are taking rifampin [48].

- **Antiseizure drugs** – The antiseizure drugs phenytoin and carbamazepine induce metabolism of methadone. In one study, nonpregnant, methadone-maintained individuals experienced withdrawal symptoms within three to four days of starting phenytoin [50]; a similar response is likely in pregnant women.

- **Antiretroviral drugs** – Methadone increases blood levels of zidovudine and may require a 50 percent reduction of the usual dose [5]. Methadone can also decrease concentrations of didanosine and stavudine. Delavirdine may increase methadone concentrations. Darunavir, efavirenz, nelfinavir, nevirapine, and lopinavir/ritonavir all have the potential to reduce serum methadone concentrations, which could result in methadone withdrawal symptoms and necessitate a methadone dose increase.

- **Other** – The H2 antagonist cimetidine and the antifungal medication ketoconazole increase methadone levels [26].

**Intrapartum and postpartum dosing** — The patient's usual oral methadone dose is continued intrapartum and postpartum [21]. Although postpartum over-sedation is a theoretic concern since methadone levels may increase as plasma volume and hepatic clearance return to the prepregnant state, we have not observed any cases of oversedation. An alternative approach is to reduce the methadone dose by 20 to 40 percent immediately postpartum [51].

In a study of 101 methadone-maintained pregnant women followed for 12 weeks after delivery, the mean dose change was -3.7 mg (-6.3 to -1.1 mg) and 5.6 over-sedation events occurred per 10,000 dosing days [52].

**Breastfeeding** — Breastfeeding should be encouraged in women who are stable on methadone and not using nonprescription opioids or misusing other prescription drugs, unless other contraindications exist [53]. This recommendation is supported by guidelines from the American College of Obstetricians and Gynecologists and the Academy of Breastfeeding Medicine [54] and apply to women who are enrolled in a methadone program on any dose of methadone. Some of the benefits include improved maternal-infant attachment and favorable effects on NAS [55-58]. It is not clear whether the favorable effects of breastfeeding on NAS are related to breast milk, skin-to-skin contact, or the act of breastfeeding since the amount of methadone in breast milk is small [59]. (See "Infant benefits of breastfeeding" and "Maternal and economic benefits of breastfeeding".)

Neonatal plasma concentrations of methadone are not related to maternal methadone dose [56]. The estimated dose of methadone in breast milk is 1 to 3 percent of the maternal weight-adjusted dose [60]. Infants who are exposed to methadone in utero remain at risk for withdrawal symptoms even while being breastfed by mothers receiving methadone [61]. In very rare cases, children exposed to methadone in breast milk are at risk of serious side effects including severe respiratory depression, heart problems, and death [62,63].

**Weaning** — NAS has been rarely reported within the first five weeks after birth when breastfeeding was abruptly discontinued [64]. There is no evidence that it occurs with gradual reduction of breastfeeding. (See "Neonatal abstinence syndrome", section on 'Feeding'.)

**Pregnancy outcome** — There is ongoing debate about whether intrauterine exposure to methadone results in long-lasting effects for the infant. However, the available data, discussed below, are generally reassuring. According to the Substance Abuse and Mental Health Services Administration, the benefits of pharmacotherapy for OUD during pregnancy outweigh the risks of untreated OUD [65].

**Congenital anomalies** — Methadone is not clearly associated with any structural birth defect [65]. In a 2016 systematic review comparing methadone versus buprenorphine treatment of pregnant women with OUD (one randomized trial [131 neonates] and four observational studies [933 neonates]), there was no significant difference in risk of congenital anomalies between the two treatments, and the overall risk of anomalies was similar to that in the general obstetric population [66].

While some individual studies have described birth defects, there is no clear pattern of anomalies [67]. Additionally, the available information is complicated by multiple confounders including maternal use of nonprescription opioids, use/misuse of other prescription medications, other illicit drug use, high smoking rates, poor nutrition, increased prevalence of infection, poor engagement with antenatal care, and complicated psychosocial circumstances. Other methodologic issues include lack of an appropriate control group, failure to provide adequate details about timing of exposure, and poor characterization of anomalies. Most studies used a cross-sectional study design, which cannot show causation.

Several studies have reported an association between methadone exposure and Pierre Robin sequence (PRS) [68-70]. The largest of these used data from 12 European Surveillance of Congenital Anomalies (EUROCAT) registries covering nearly four million births [69]. The odds for PRS were odds ratio 15.5 (95% CI 6.1-33.3); however, the study was unable to show causation due to potential confounding factors such as alcohol use and smoking, which are similarly associated with PRS. Regardless, the prevalence of PRS is very low (<1/10,000 births), so the

possible absolute increase in PRS with methadone exposure is small and should be balanced against the risk of untreated OUD during pregnancy, which has well-described adverse consequences.

### Other fetal and neonatal effects

**Thyroid** — Enlargement of the fetal thyroid has been reported in methadone-exposed infants, possibly due to changes in monoamine neurotransmitter systems [71]. The functional significance of this enlargement is unclear.

**Prolonged QTc** — QTc intervals >450 milliseconds have been reported in 15 to 19 percent of methadone-exposed neonates. All resolved by seven days without cardiac events [47,72].

**Visual development** — Several studies have suggested that prenatal exposure to methadone may result in abnormal visual development. In a systematic review of 12 studies that reported visual outcomes in offspring of women prescribed methadone in pregnancy (275 methadone-exposed versus 128 unexposed), the prevalence of childhood strabismus and nystagmus in the methadone-exposed population was approximately 50 percent, which was higher than expected; differences in visual evoked potentials (VEPs) were also noted [73]. In one of the included studies, the majority (70 percent) of infants with prenatal exposure to methadone demonstrated some type of visual disturbance [74].

Most studies lacked sufficient information to adequately control for other prenatal exposures, thus limiting the ability to make any conclusion about causation. The prevalence of tobacco use among women with OUD is >90 percent. Like methadone, prenatal exposure to tobacco and other illicit drugs (eg, cocaine, amphetamines) has also been associated with ophthalmic abnormalities [75]. Maternal smoking increases the risk for optic nerve hypoplasia and also results in a significantly thinner retinal nerve fiber layer [76]. Additionally, a study found that strabismus increased proportionally with the amount of cigarettes smokes, reaching a relative risk of 1.9 (95% CI 1.57-2.30) at >10 cigarettes/day [77].

The long-term significance of these findings is unclear. In at least one study, differences in VEPs in infants born to women with OUD-prescribed methadone remained after adjusting for tobacco use [74]. In another study, the findings were transient: In 36-month old children, there was no difference in VEPs between children exposed to methadone and a group of unexposed children [78].

**Size and gestational age at birth** — Methadone pharmacotherapy has been associated with an increased risk of adverse neonatal outcomes, such as preterm birth <32 weeks of gestation, small for gestational age infants, low birth weight, decreased head circumference, and

sequelae often associated with these outcomes: jaundice, thrombocytosis, and admission to a neonatal intensive care unit [68,79]. However, methadone pharmacotherapy appears to improve birth weight compared with women using nonprescription opioids, even if not quite to the birth weights seen in the general population (mean difference -295 g).

The association between in utero exposure to methadone and adverse outcome is somewhat explained by confounders such as race, body mass index, gestational weight gain, cigarette smoking, socioeconomic deprivation, maternal age, and parity [68,80-83]. Although some studies have reported that daily doses of 80 to 160 mg adversely affected fetal growth, these findings have not been consistent across studies and could have been due to confounders [18,39,84,85].

**Neonatal abstinence syndrome** — Newborns who withdraw from opioids present with a well-recognized constellation of signs and symptoms known as NAS. Withdrawal from methadone usually occurs 48 to 72 hours after birth but rarely may be delayed by up to a month [86,87]. The relationship between maternal methadone dose and neonatal withdrawal is controversial and limited by several study design factors, but the body of evidence suggests no correlation between methadone dose and severity of neonatal withdrawal [88]. (See "Neonatal abstinence syndrome" and "Infants of mothers with substance use disorder".)

When recognized and managed appropriately, there are no proven long-term sequelae of NAS; however, treatment often requires a lengthy neonatal intensive care unit admission (median length of stay from 13 to 19 days) and results in significant health care costs (totaling USD $1.5 billion in aggregate costs or USD $66,700 per infant with NAS [89,90]). Frequently overlooked are the significant maternal psychologic stress from feelings of guilt and sadness and delayed maternal-fetal bonding when the infant is in an intensive care unit rather than rooming in or at home.

The clinical manifestations and management of neonatal withdrawal are reviewed in detail separately. (See "Neonatal abstinence syndrome".)

**Sudden neonatal death** — Opiates have been implicated as a cause of sudden infant death [91]. A retrospective study of sudden death demonstrated an unexpectedly high proportion of neonatal deaths in which there was a maternal history of methadone use (31 percent of 32 neonatal deaths evaluated by autopsy) [92]. Many of these were also complicated by maternal nonprescription opioid use and misuse of other prescription drugs. Whether the deaths were related to methadone (possibly due to QT prolongation) or other factors (eg, exposure to parental smoking or unsafe sleeping practices) is unclear.

While not all factors are easily addressed in the short term, unsafe sleep practices (8 of 32 cases) is an opportunity for harm reduction; patients should be educated about safe sleep before being

discharged home, and the message should be reinforced at visits with a medical provider during the postpartum period. (See "Sudden infant death syndrome: Risk factors and risk reduction strategies", section on 'Sleep position and environment'.)

**Long-term outcome** — Determining the possible long-term consequences of in utero methadone exposure is complicated by a multitude of factors, including concomitant prenatal and postnatal exposures, medical factors, and sociodemographic factors, all of which have potential implications for neurodevelopmental outcome. Another limitation is the high rates of attrition (31 to 70 percent) in many studies [73].

- **Neurodevelopment** – Differences in motor performance, speech and language performance, cognitive performance, and behavior have all been reported in methadone-exposed infants and children. In a meta-analysis of childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy, compared with unexposed infants, methadone exposure was associated with a lower Mental Development Index (MDI; weighted mean difference [WMD] -4.43, 95% CI -7.24 to -1.63) and lower Psychomotor Development Index (PDI; WMD -5.42, 95% CI -10.55 to -0.28) at age two years, but no differences were seen in studies reporting MDI and PDI at age six months [73]. The authors postulated that differences often appear as children grow older.

  **Opioids (and opioid metabolites) freely cross the placenta** – Opioid receptors are present in several fetal neurologic structures from a very early gestational age. Studies demonstrating that methadone may alter development of dopaminergic, cholinergic, and serotonergic systems; myelination; and the microstructure of major white matter tracts lend biologic plausibility to the concept that in utero exposure to methadone may have adverse long-term neurodevelopmental consequences [93,94]; however, this probably applies to most, if not all, opioids and is not specific to methadone. Findings from neuroimaging studies also have significant limitations due to failure to account for polysubstance abuse, smoking, nutritional deficiency, and other antenatal and early life exposures.

- **Hospitalization** – In a registry study from the Czech Republic, hospitalization for infection, gastrointestinal, and skin diseases among children ages 0 to 3 years was higher among offspring of mothers in an opioid maintenance treatment program than those in the general population; in utero methadone exposure was associated with a higher risk of hospitalization and longer hospitalization than in utero buprenorphine exposure [95]. Notably, in the Czech Republic, methadone is available at no cost while buprenorphine may be cost-prohibitive for many patients, which introduces bias based on ability to pay.

## BUPRENORPHINE PHARMACOTHERAPY

**Provider** — In the United States, buprenorphine can be dispensed by an opioid treatment program and can be prescribed by clinicians who have undergone appropriate credentialing. A directory of providers licensed to prescribe buprenorphine is available online. It is not a complete listing because clinicians can request not to be listed.

As with methadone, successful pharmacotherapy depends upon a comprehensive, multidisciplinary, coordinated approach to care [2,3]. In contrast to methadone, which is typically administered at a comprehensive treatment center (ie, availability of pharmacotherapy along with social work and psychiatry), buprenorphine is typically prescribed in the office of the credentialed clinician, unless the patient is admitted for opioid withdrawal and/or to coordinate outpatient treatment. If prenatal care is not available onsite at the office, then these services will need to be arranged separately [24,28,96].

**Pharmacology** — Buprenorphine acts as a partial agonist at the mu-opioid receptor and has a prolonged duration of action due to its high affinity for the receptor. It is also an antagonist at the kappa opioid receptor. Pharmacologic effects are similar to full opioid agonists (eg, morphine, methadone), but with a "ceiling effect" at high doses across a range of pharmacodynamic measures [97]. This lowers the potential for adverse effects from overdose (eg, respiratory depression), but could also explain why there is greater treatment retention with methadone, especially compared with certain buprenorphine doses/dosing regimens.

Buprenorphine suppresses withdrawal for 24 to 48 hours; typical dosing for OUD is every 24 hours [98,99]. Peak plasma levels occur at approximately 90 minutes and increase linearly with increasing dose. The drug is highly lipophilic, 96 percent bound to plasma proteins, and metabolized by the liver with an active metabolite, norbuprenorphine [99]. It is primarily metabolized by the cytochrome P450 enzyme pathway.

Lower maximum plasma buprenorphine concentrations and total 24-hour plasma levels have been demonstrated during pregnancy compared with the postpartum period [100]. In one study, some women with OUD excreted a higher percentage of their daily buprenorphine dose during pregnancy than postpartum, indicating possible enhanced renal elimination antenatally [101]. Most of the study participants were prescribed a higher buprenorphine dose as pregnancy progressed.

Buprenorphine and its pharmacologically active metabolites cross the placenta [102,103]. In a study of women with OUD receiving maintenance doses of buprenorphine, mean cord/maternal ratios for buprenorphine and norbuprenorphine were 0.43 and 0.53, respectively [103].

Transplacental transfer and metabolism do not appear to differ significantly in preterm placentas [104].

**Formulations and administration** — Buprenorphine is available in a variety of forms and is available with and without naloxone. In the United States, formulations approved by the US Food and Drug Administration include sublingual tablets, film, buccal film, implant, and an extended-release injection. Sublingual, or buccal, formulations have significantly greater bioavailability compared with oral administration and are the most common formulation used during pregnancy.

Proper use of buprenorphine films or tablets is important to ensure absorption; misuse may result in lower bioavailability and consequently lower peak concentrations/effect. Patients should be instructed to drink water to moisten the mouth before taking buprenorphine. Buprenorphine is placed under the tongue (left or right side) or inside the cheek depending on prescribed route of administration and kept in place until completely dissolved, which typically takes 30 minutes. Buprenorphine should not be chewed or swallowed. Eating, drinking, and/or smoking cigarettes should be avoided until the medication has fully dissolved.

Buprenorphine has been available as an implant (Probuphine) since 2016 and a monthly extended-release subcutaneous injection since 2017. There are no adequate or well-controlled studies of these formulations in pregnant women; however, the risks should be comparable to buprenorphine in other forms. We do not recommend implant removal in women who conceive while using it; however, they should be closely monitored for symptoms. In this situation, additional buprenorphine may be required to augment therapy.

The implant is indicated for patients with sustained clinical stability on no more than 8 mg of buprenorphine. It is worth noting that many medications, including buprenorphine, require dose adjustments during pregnancy; however, the dose of the implant cannot be changed [105].

**Initial and maintenance dosing**

- **When to start** – Because it is a partial agonist at the mu-opioid receptor, initiation of buprenorphine may lead to withdrawal symptoms in patients who have recently used opioids. To minimize this risk, it should be initiated when a woman begins to show objective, observable signs of moderate withdrawal (table 3), usually six hours or longer after the last dose of a short-acting opioid, and potentially longer (24 hours to 48 hours) following the use of long-acting opioids [106,107], but before severe withdrawal symptoms occur.

  Bothersome mild withdrawal symptoms during this time can be treated with a variety of over-the-counter and prescription medications, such as acetaminophen for aches, antacids for indigestion, loperamide for diarrhea, and hydroxyzine or diphenhydramine for anxiety and

restlessness [107]. Alternatively, clonidine can also be prescribed. (See "Opioid withdrawal in the emergency setting", section on 'Management' and 'Starting dose in hospitalized women' above.)

- **Initial dosing** – There is no consensus on the optimal method of induction of buprenorphine during pregnancy [106-108]. Our approach for initial and subsequent dosing is the same as that in nonpregnant women: A typical starting dose for buprenorphine is 2 to 4 mg given sublingually. After two hours of observation, if withdrawal symptoms remain, an additional 2 to 8 mg of buprenorphine can be administered.

  On the following day, the patient is given a single dose consisting of the total of the doses received the first day (up to 8 mg). Following observation for residual withdrawal symptoms, the dose may be increased in 4 mg increments, up to a maximum of 16 mg total during initial stabilization. Most patients will stabilize on 8 to 16 mg/day [109], so the dose should not be increased above 16 mg for several days to allow time to reach pharmacologic steady state. (See "Pharmacotherapy for opioid use disorder", section on 'Buprenorphine'.)

  One study observed that buprenorphine is cleared more extensively by pregnant than postpartum women [110], and some authors have suggested three or four times daily dosing may be required in pregnant women to sustain plasma concentrations [105].

- **Maintenance dosing** – Some authors have suggested that unlike methadone, women maintained on buprenorphine typically do not require large dose adjustments during pregnancy [106]. However, data from three randomized trials [111-113] demonstrated the need for buprenorphine dose adjustments throughout pregnancy; the average increase was 3 mg [108].

**Patients with hepatic or renal insufficiency** — Buprenorphine is primarily metabolized by the liver, so severe hepatic dysfunction is a contraindication to buprenorphine use. Lesser degrees of hepatic dysfunction may impair buprenorphine metabolism; in these women, a reduction in dose or the frequency of administration may be necessary. In women with a history of hepatic dysfunction, liver enzymes should be monitored because buprenorphine can cause significant elevations in aspartate aminotransferase and alanine aminotransferase [114,115].

If possible, liver function tests are obtained at baseline, but waiting for the results should not delay treatment [116]. The tests should be repeated periodically during treatment. There is no evidence to guide the frequency of monitoring, but semi-annual testing is adequate for most women. Signs of hepatotoxicity (eg, fever, malaise, nausea/vomiting) should prompt additional testing.

In women with laboratory evidence of hepatotoxicity (transaminase levels >3- to 5-fold higher than

normal), all possible causes of liver injury should be evaluated and consideration should be given to lowering the dose or discontinuing buprenorphine [117].

Some authors believe that buprenorphine doses do not need to be adjusted in patients with renal failure [114,115]; however, manufacturers suggest caution when dosing patients with severe renal failure (creatinine clearance <30 mL/min), or slow titration of doses until dose stabilization [118-120].

**Missed dose** — Women may present to the labor and delivery unit requesting buprenorphine because of a "lost" or "stolen" dose. In this case, efforts should be made to contact their prescriber to confirm dosing and follow-up. If the provider cannot be reached and assistance from a clinician with experience in this area is not available, a careful history should be obtained to look for any suggestion of drug diversion or nonprescription opioid use as well as obtaining a urine drug screen. A physical examination should be performed to evaluate for signs of intoxication/overdose or withdrawal (eg, Clinical Opiate Withdrawal Scale score), and urine toxicology should be sent. (See "Acute opioid intoxication in adults", section on 'Clinical features of overdose' and "Medically supervised opioid withdrawal during treatment for addiction".)

In the absence of evidence of other opioid use, a single missed dose of buprenorphine can be replaced safely, and the normal dose resumed. Prescription drug monitoring programs exist in every state except Missouri. Many will include recent prescriptions for controlled substances including buprenorphine, and dose can often be confirmed this way. If the dose is not available, or there is any concern, a test dose of 2 mg can be given before resuming the patients previous dose two hours later, if there is no evidence of sedation (see 'Initial and maintenance dosing' above). The woman should only be given a single dose and then referred to her usual buprenorphine provider for further management. A period of brief observation may be considered. There is no requirement for fetal assessment in the absence of other indications, though some centers routinely obtain a nonstress test or biophysical profile on all women presenting to labor and delivery unit triage at or beyond viability.

**Urine drug testing** — Although patients on methadone are supposed to have at least eight urine drug screening tests (UDS) per year, testing for those on buprenorphine is performed as clinically appropriate [36]. The frequency of UDS to monitor adherence to therapy and continued nonprescription opioid use varies by phase of treatment. Early in treatment, UDS may be performed every one to two weeks and then at least monthly during maintenance treatment.

A specialized assay can be ordered to detect buprenorphine since it is often not detected by standard UDS, which identifies naturally occurring opiates and their metabolites. However, an increasing number of UDS are able to detect buprenorphine, so providers should be familiar with

the tests available in their location.

**When to check buprenorphine levels** — Buprenorphine levels are not used to guide dosing. A quantitative buprenorphine urine level can be obtained to verify buprenorphine use but can be falsified by adding pieces of buprenorphine tablets to the urine. If tampering is suspected, then the urine should be tested for buprenorphine metabolites (eg, norbuprenorphine).

**Side effects** — Common side effects include chills, fever, abdominal pain, vasodilation, withdrawal, constipation, nausea, vomiting, diarrhea, insomnia, and anxiety. Like other opioids, buprenorphine may cause respiratory depression, particularly when taken with benzodiazepines or other central nervous system depressants [121]. Acute hepatotoxicity has been reported rarely in patients with OUD treated with buprenorphine.

Because it is a partial agonist at the mu-opioid receptor, initiation of buprenorphine may lead to withdrawal symptoms in patients with OUD, particularly if it is given within six hours of opioid use [118].

**Drug and chemical interactions** — Buprenorphine has fewer drug interactions compared with methadone [122,123]. It does not increase the QT interval to any clinically meaningful degree. A brief synopsis of drug interactions follows; more information is available in the Lexicomp drug interactions program.

- Because it is primarily metabolized by the cytochrome P450 enzyme pathway, close monitoring for withdrawal symptoms is recommended for buprenorphine-maintained patients who are started on CYP3A4 inducers (eg, rifampicin, phenobarbital, carbamazepine), as dose increases may be required. In contrast, dose reduction may be required if CYP3A4 inhibitors (eg, ketoconazole, gestodene, clarithromycin, and some HIV protease inhibitors) are used concomitantly with buprenorphine.

- Although there may be a theoretical risk of additive central nervous system and/or cardiorespiratory depressive effects with combined use of opioids and high doses of magnesium sulfate (as used for prevention of eclampsia or for neuroprotection), we have neither observed nor read case reports of such adverse drug interactions and do not alter dosing in patients receiving both drugs during labor.

- Benzodiazepines, and other sedative hypnotics, may act synergistically with buprenorphine. As with methadone, co-prescribing buprenorphine with benzodiazepines may increase the risk of respiratory difficulties, coma, or death [124]; carefully tapering benzodiazepines is recommended.

**Intrapartum and postpartum dosing** — Women admitted in labor or before scheduled cesarean delivery should continue to receive their full daily buprenorphine dose. Discontinuation exposes the mother and fetus to the potential risks of withdrawal. Furthermore, discontinuation can precipitate withdrawal symptoms during reintroduction of buprenorphine in postpartum patients receiving opioid analgesics for pain control [125].

Buprenorphine maintenance therapy is usually dosed once daily; women taking divided doses should continue taking their buprenorphine as prescribed. Doses of buprenorphine and other prescribed opioids should be verified when possible, especially on admission to labor and delivery. Verification can be accomplished by querying the prescription monitoring program database; however, when dose verification is not possible, such as in an emergency, the reported daily opioid dose can be given in two to four divided doses while monitoring for sedation and respiratory depression [126]. This approach may also be useful when there is concern about whether the woman is taking her entire prescribed dose [126].

If the buprenorphine dose was increased during pregnancy, the need to continue this increased dose should be assessed postpartum. However, most women who undergo buprenorphine maintenance therapy will not experience large dose adjustments during their pregnancies and may continue the same doses after delivery [105,127].

**Breastfeeding** — Several guidelines from national organizations have considered use of buprenorphine pharmacotherapy compatible with breastfeeding [21,64,128-130]. The drug's poor bioavailability when taken orally means it is unlikely that significant absorption will occur from intake of breast milk. Based on data from a few small series, a breastfed infant would receive <1 percent of the maternal weight-adjusted dose [130]. The small amounts of buprenorphine in human milk are unlikely to have short-term negative effects on the developing infant [131]. However, breastfed infants should be monitored for respiratory difficulty, sedation, appropriate feeding, and attainment of developmental milestones, especially in younger, exclusively breastfed infants [64,130].

Pregnant women taking the combination buprenorphine/naloxone can be encouraged to breastfeed; although no human safety data are available, neonatal effects are unlikely based upon the limited bioavailability of naloxone [132]. (See 'Use of combined buprenorphine plus naloxone formulation' below.)

**Weaning** — A single case of infant withdrawal symptoms after sudden cessation of breastfeeding has been reported [133]. Despite the low risk, abrupt cessation of breastfeeding is not recommended [134]. Women who wish to discontinue breastfeeding are advised to gradually wean the infant from breast milk over a period of two weeks. (See "Neonatal abstinence

syndrome", section on 'Feeding'.)

**Pregnancy outcome** — There is ongoing debate about whether intrauterine exposure to buprenorphine or buprenorphine/naloxone results in long-lasting effects for the infant. However the available data, discussed below, are generally reassuring. According to the Substance Abuse and Mental Health Services Administration, the benefits of pharmacotherapy for OUD during pregnancy outweigh the risks of untreated OUD [65].

As discussed above, studies assessing the impact of buprenorphine on pregnancy outcomes are limited by a multitude of factors, including concomitant exposures to medications and illicit drugs, comorbidities, nutritional factors, and sociodemographic factors, which may confound any association between buprenorphine and adverse pregnancy outcomes.

**Congenital anomalies** — Studies of buprenorphine use in pregnancy have not demonstrated an increased risk of birth defects [135].

- A 2016 systematic review including one randomized trial (131 neonates) and four observational studies (933 neonates) comparing methadone versus buprenorphine treatment of pregnant women with OUD found no significant difference in risk of congenital anomalies between the two treatments, and the overall risk of anomalies was similar to that in the general obstetric population [66]. These data, although reassuring, are insufficient to determine whether either drug is associated with an increased risk of congenital anomalies. Most of the included studies had a medium to high risk of bias, poorly characterized reported defects, failed to describe relevant confounders (maternal use of nonprescription opioids and other substance use, alcohol, and cigarettes; poor maternal nutrition; increased prevalence of maternal infection) or provide adequate details about timing of exposure, and may have missed anomalies not previously known or immediately apparent at birth.

- A study restricted to analysis of congenital anomalies among pregnancies exposed to buprenorphine in the first trimester reported an 8.4 percent rate of anomalies (prevalence ratio compared with no opioid use in pregnancy 2.0, 95% CI 1.2-3.2) [136].

Although concerns about the effects of methadone on the developing visual system have been raised (see 'Other fetal and neonatal effects' above), buprenorphine exposure does not appear to confer this risk [78]. There are no data on the effect on the thyroid in humans.

**Neonatal effects**

**Size and gestational age at birth** — Compared with infants born to nonopioid-dependent women, neonates exposed in utero to buprenorphine appear to exhibit lower birth weight and

smaller head circumference [137,138]. Several observational and randomized studies have demonstrated longer gestation, increased birth weight, and larger head circumference in buprenorphine-exposed versus methadone-exposed pregnancies [66,139].

These are interrelated variables (ie, larger head circumference may be the result of later gestational age at birth), and most studies were limited in their ability to control for confounding factors (eg, prior obstetric history, smoking, etc). Other large studies have not consistently confirmed a difference in these outcomes [140-142].

**Neonatal abstinence syndrome** — Interest in buprenorphine as an alternative to methadone stems from data showing a lower rate of neonatal withdrawal (neonatal abstinence syndrome [NAS]), which has been attributed to its lower bioavailability, lower transplacental passage, and greater affinity to binding to the mu-opioid receptor but with less intrinsic activity than methadone [106,108].

Data regarding the relationship between the maternal dose of buprenorphine and need for treatment of NAS remain conflicting [143,144]. Quantification of buprenorphine in meconium samples of 10 infants born to buprenorphine-treated women demonstrated that neither cumulative nor total third-trimester buprenorphine exposure predicted meconium concentrations or infant outcomes [145]. However, there was a possible relationship between meconium buprenorphine concentrations and the onset of NAS.

In a study of 41 women entering treatment at a specialized treatment program for pregnant women, both maternal buprenorphine dose and prenatal polysubstance exposure to illicit substance use/licit substance misuse were independently associated with NAS expression [144]. Polysubstance exposure was associated with more severe NAS expression after controlling for the effects of buprenorphine dose, but unlike with methadone, severity was not related to either cigarette or selective serotonin reuptake inhibitor use.

**Long-term outcome** — There are few long-term neurodevelopmental studies of buprenorphine-exposed fetuses [141,146-149]. The lack of such studies documenting absence of adverse long-term effects should be discussed with women contemplating buprenorphine maintenance therapy [21]. Most of the available data come from small retrospective series lacking comparisons with existing treatments, untreated women with OUD, or normal controls; therefore, the ability to address confounding factors is limited (especially exposure to other substances). Research on long-term neurodevelopmental outcome is further limited by high rates of attrition, heterogeneity in the methods of assessment, and length of follow-up.

- Cognitive and motor development.

- One study (n = 21 children) reported lower scores on cognitive and language scales at three years of age in children exposed prenatally to maternal buprenorphine use compared with nonexposed controls [146].
- A longitudinal study, which included 73 children evaluated at 24 months (n = 24 buprenorphine exposed, n = 19 methadone exposed, n = 30 nonexposed controls) found no differences between groups in neurologic development or temperament during the first two years of life [141].
- A retrospective study observed that in utero exposure to maternal methadone dose >100 mg/day was associated with a reduction in infant head circumference compared with buprenorphine or lower dose methadone; it also appeared to have a negative impact on motor skill development during early infancy [150], but others have not confirmed this finding [151].

- Brain imaging and EEG.
  - A small series reported no structural or signal abnormalities on neonatal magnetic resonance imaging in seven infants exposed in utero to buprenorphine pharmacotherapy [147].
  - A small series reported no abnormalities on electroencephalography (n = 9 neonates) or cranial ultrasound (n = 10 neonates) born to women on buprenorphine pharmacotherapy [148].

## SPECIAL ISSUES

**Preconception pharmacotherapy** — Conceiving while on methadone has been associated with better drug treatment outcomes compared with women who initiate methadone during pregnancy [41].

**Switching from methadone to buprenorphine therapy** — We agree with the American College of Obstetricians and Gynecologists' recommendation against transitioning women from methadone to buprenorphine before or during pregnancy [21]. If a woman desires to switch, this should be managed by clinicians with appropriate expertise and preferably prior to conception and following an established protocol [152].

There is no compelling reason to switch women already on methadone to buprenorphine either before or during pregnancy. Transition from methadone to buprenorphine introduces the possibility

for destabilization [107,153]. Transfer from methadone or other long-acting opioids can induce withdrawal symptoms and cause transient dysphoria, although transfer from short-acting opioids appears to be safe [154].

**Switching from buprenorphine to methadone therapy** — There is no compelling reason to switch women from buprenorphine to methadone who are stable on treatment and who are trying to conceive or are pregnant. According to the World Health Organization guidelines for pharmacologic treatment of opioid dependence: If women are being successfully treated with buprenorphine, then the benefit of staying with a treatment that is working should be taken into consideration [155]. However, continued opioid withdrawal symptoms or opioid craving/recidivism may suggest a poor response to buprenorphine. In these women, switching from buprenorphine to methadone may be reasonable.

**Use of combined buprenorphine plus naloxone formulation** — Buprenorphine is also available in combination with naloxone in a 4:1 ratio. The naloxone combination product is intended to deter intravenous abuse of the sublingual formulation because crushing and injecting the combination formulation causes withdrawal symptoms, which do not occur when the tablet or filmstrip is taken orally or sublingually [156]. However, actual deterrence has not been proven. (See "Pharmacotherapy for opioid use disorder", section on 'Transmucosal'.)

Buprenorphine/naloxone has been the predominant formulation used in the United States because of the perceived benefits of reduced diversion and misuse and limited access to alternative agents in some areas. The available experience with buprenorphine/naloxone use during pregnancy has been reassuring. Four studies including a total of 118 women reported no significant differences in maternal or neonatal outcomes compared with use of buprenorphine alone or methadone, but these studies are limited by small sample size and lack of control for confounders such as exposure to other drugs [157-160]. Long-term follow-up studies of neurodevelopmental outcome are not available. In animal studies naloxone was not associated with an increased risk of congenital anomalies. Naloxone is not detectable in the blood when taken orally and is only detectable at low levels (10 percent) when taken sublingually.

Previous guidelines recommended use of the buprenorphine monoproduct because of theoretical risks of naloxone exposure and withdrawal from misuse, but these risks are not supported by the available data. However, the monoproduct has a higher potential for diversion and misuse, and a higher street value, when compared with the combination product [21]. While there is still some disagreement among experts, based on reassuring results from some studies, use of the combination product during pregnancy will likely expand [21,116].

There is no reason to preferentially start pregnant women on the monoproduct, or switch to the

monoproduct in women who were previously stable on the combination product, although switching was advised in the past. Prescribing decisions should be made with the patient's informed consent after review of the risks and benefits [116].

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Maternal medical complications".)

## SUMMARY AND RECOMMENDATIONS

- The advantages and disadvantages of methadone versus buprenorphine pharmacotherapy of opioid use disorder (OUD) are compared in the tables (table 1 and table 5). (See "Overview of management of opioid use disorder during pregnancy", section on 'Methadone or buprenorphine pharmacotherapy?'.)

**Methadone**

- We begin methadone therapy in an inpatient setting with a single oral dose of methadone 20 to 30 mg for most symptomatic women. After the initial methadone dose, incremental doses of 5 to 10 mg are administered every three to six hours as needed to treat withdrawal symptoms. After initial stabilization, the patient is discharged, and the methadone dose is increased in 5 to 10 mg increments per week, if indicated, to maintain the lowest dose that controls withdrawal symptoms and minimizes the desire to use additional opioids. In our experience, the average dose is approximately 120 mg. (See 'Initial dosing' above and 'Maintenance dosing after hospital discharge' above.)

- With advancing gestational age, plasma levels of methadone progressively decrease and clearance increases so that the half-life falls from an average of 22 to 24 hours in nonpregnant women to 8 hours in pregnant women. (See 'Pharmacology' above.)

- Opioid withdrawal symptoms mimic common discomforts of pregnancy (nausea, vomiting, low back pain), which should be taken into account before increasing the daily methadone dose. (See 'Maintenance dosing after hospital discharge' above.)

- Twice-daily dosing at 12-hour intervals (or rarely, three times daily at 8-hour intervals) results in more sustained plasma levels, fewer withdrawal symptoms, less illicit drug use, and less effect on fetal behavior than a single high methadone dose. However, split dosing is not

possible for all women because it requires that she is a candidate for take-home doses. (See 'Split dosing' above.)

- Weekly urine drug screens are performed to monitor for continued nonprescription opioid use and prescription medication misuse. (See 'Urine drug testing' above.)
- Methadone levels are unnecessary in asymptomatic women. We check a methadone serum trough level in the symptomatic women with a negative urine drug screen who are excessively sedated or symptomatic despite an increase in methadone dose. These women may benefit from split dosing. (See 'When to check methadone levels' above and 'Split dosing' above.)
- The patient's usual methadone dose should be continued intrapartum. This dose may be continued immediately postpartum or tapered by 20 to 40 percent. (See 'Intrapartum and postpartum dosing' above.)
- Methadone can prolong the QT interval and cause torsades de pointes. (See 'Side effects' above.)
- Women are encouraged to breastfeed. Women who wish to discontinue breastfeeding should be advised to gradually wean the infant from breast milk over a period of two weeks to reduce the risk of neonatal withdrawal. (See 'Breastfeeding' above and 'Weaning' above.)

**Buprenorphine**

- Buprenorphine can only be prescribed by clinicians who have undergone appropriate credentialing. (See 'Initial and maintenance dosing' above.)
- To minimize the risk of buprenorphine-induced withdrawal symptoms, it should only be initiated when a woman shows objective, observable signs of moderate opioid withdrawal (table 3), usually 6 hours or longer after the last dose of a short-acting opioid, and potentially longer (24 to 48 hours) following the use of long-acting opioids. (See 'Initial and maintenance dosing' above.)
- Drug dosing for buprenorphine is similar to that in nonpregnant women. Standard induction protocols, such as the one described above, can be used. Dose adjustments may be needed with advancing gestational age; the average increase appears to be approximately 3 mg. (See 'Initial and maintenance dosing' above.)
- The patient's usual buprenorphine dosing should be maintained intrapartum and postpartum. (See 'Intrapartum and postpartum dosing' above.)

- There is no reason to preferentially start pregnant women on the buprenorphine monoproduct or switch to the monoproduct in women who were previously stable on the buprenorphine/naloxone combination formulation, as had been advised in the past. (See 'Use of combined buprenorphine plus naloxone formulation' above.)
- Women are encouraged to breastfeed. Women who wish to discontinue breastfeeding are advised to gradually wean the infant from breast milk over a period of two weeks to reduce the risk of neonatal withdrawal. (See 'Breastfeeding' above.)



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Topic 87238 Version 32.0

## GRAPHICS

### Pros and cons of buprenorphine versus methadone pharmacotherapy in pregnancy

| Pros |
|---|
| ▪ Lower risk of overdose |
| ▪ Fewer drug interactions |
| ▪ Ability to be treated in a private office setting without the need for daily visits to a licensed treatment program |
| ▪ Dosing of buprenorphine is similar to that in nonpregnant women |
| ▪ Insurance in the United States may cover buprenorphine prescribed by a private physician in an office setting, while not covering methadone dispensed in a licensed opioid treatment program |
| ▪ Fewer side effects |
| ▪ Low risk of adverse cardiovascular side effects (by contrast, methadone is associated with small increase in risk of arrhythmia) |
| ▪ For the newborn, in utero exposure to buprenorphine rather than methadone may result in a lower risk of preterm birth, higher birth weight, larger head circumference, and a lower rate and severity of neonatal withdrawal |
| **Cons** |
| ▪ Relative to methadone, fewer data are available on pregnancy outcomes after first trimester exposure |
| ▪ Lack of long-term neurodevelopmental outcome data |
| ▪ Clinically important patient dropout rate due to dissatisfaction with the drug |
| ▪ More difficult induction protocol with the potential risk of precipitated withdrawal |
| ▪ Increased risk of diversion* (especially the buprenorphine monotherapy formulation) |
| ▪ Less stringent structure of some office-based treatment programs |
| ▪ Reports of maternal hepatic dysfunction and elevated transaminases |
| ▪ Effects of buprenorphine are only partially reversible by naloxone |
| ▪ The maximum daily dose of buprenorphine is 32 mg, due to a ceiling effect, which may not be sufficient in all women (usually those requiring more than 140 mg per day of methadone) |
| ▪ More expensive than methadone |
| ▪ Treatment with methadone may result in greater reduction in illicit opioid use |

* Diversion is the unauthorized rerouting or misappropriation of prescription medication to someone other than for whom it was intended.

*Adapted from:*


1. *ACOG Committee on Health Care for Underserved Women, American Society of Addiction Medicine. ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. Obstet Gynecol 2012; 119:1070.*
2. *Young JL, Martin PR. Treatment of opioid dependence in the setting of pregnancy. Psychiatr Clin North Am 2012; 35:441.*
3. *Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010; 363:2320.*
4. *Peddicord AN, Bush C, Cruze C. A comparison of suboxone and methadone in the treatment of opiate addiction. J*

*Addict Res Ther 2015; 6:248.*

Graphic 87713 Version 12.0

## DSM-5 diagnostic criteria for other (or unknown) substance use disorder

A problematic pattern of use of an intoxicating substance not able to be classified within the alcohol; caffeine; cannabis; hallucinogen (phencyclidine and others); inhalant; opioid; sedative, hypnotic, or anxiolytic; stimulant; or tobacco categories and leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for other (or unknown) substance (refer to Criteria A and B of the criteria sets for other [or unknown] substance withdrawal, p. 583).
    b. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

**Specify if:**

**In early remission:** After full criteria for other (or unknown) substance use disorder were previously met, none of the criteria for other (or unknown) substance use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use the substance," may be met).

**In sustained remission:** After full criteria for other (or unknown) substance use disorder were previously met, none of the criteria for other (or unknown) substance use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use the substance," may be met).

**Specify if:**

**In a controlled environment:** This additional specifier is used if the individual is in an environment where access to the substance is restricted.

**Coding based on current severity:** Note for ICD-1-CM codes: If an other (or unknown) substance intoxication, other (or unknown) substance withdrawal, or another other (or unknown) substance-induced mental disorder is present, do not use the codes below for other (or unknown) substance use disorder. Instead, the comorbid other (or unknown) substance use disorder is indicated in the 4th character of the other (or unknown) substance-induced disorder code (see the coding note for other (or unknown) substance intoxications, other (or unknown) substance withdrawal, or specific other (or unknown) substance-induced mental disorder). For example, if there is comorbid other (or unknown) substance-induced depressive disorder and other (or unknown) substance use disorder, only the other (or unknown) substance-induced depressive disorder code is given, with the 4th character indicating whether the comorbid other (or unknown) substance use disorder is mild, moderate, or severe: F19.14 for other (or unknown) substance use disorder with the other (or unknown) substance-induced depressive disorder or F19.24 for a moderate or severe other (or unknown) substance use disorder with other (or unknown) substance-induced depressive disorder.

**Specify current severity:**

**305.9 (F19.1) Mild:** Presence of 2–3 symptoms.

| |
|---|
| **304.9 (F19.2) Moderate:** Presence of 4–5 symptoms. |
| **304.9 (F19.2) Severe:** Presence of 6 or more symptoms. |



Graphic 50295 Version 10.0

## Maternal opioid withdrawal symptoms

| Opioid withdrawal signs and symptoms |
|---|
| **Mild withdrawal signs and symptoms include** |
| Generalized anxiety, irritability |
| Opioid craving |
| Restlessness |
| Slight aching of muscles, joints, and bones |
| Generalized pain |
| Lower back pain |
| **Mild to moderate withdrawal signs and symptoms include** |
| Tension |
| Restless sleep |
| Mydriasis |
| Lethargy |
| Diaphoresis |
| **Moderate withdrawal signs and symptoms include** |
| Chills alternating with flushing and diaphoresis |
| Nausea and/or stomach cramps |
| Rhinorrhea |
| Moderate aching of muscles, joints, and bones |
| Anorexia |
| Yawning |
| Lacrimation |
| Goose flesh (earlier if client is in a cold, drafty room) |
| Elevated pulse and blood pressure |
| **Moderate to severe withdrawal signs and symptoms include** |
| Diarrhea |
| Vomiting |
| Tremors |
| Tachycardia (pulse over 100 beats per minute) |
| Increased respiratory rate and depth |
| **Severe withdrawal signs and symptoms include** |
| Doubling over with stomach cramps |
| Kicking movements |
| Elevated temperature (usually low grade, less than 100°F) |

Note: Withdrawal signs and symptoms differ in their order of appearance from one individual to another. Some individuals may not exhibit certain withdrawal signs and symptoms. Signs may also include uterine irritability, increased fetal activity, or, rarely, hypotension.

*Reproduced from: Alcohol and other drug treatment guidelines for pregnant, substance-using women. In: Treatment Improvement Protocol Series 2: Pregnant, Substance-abusing Women, Mitchell JL (Ed), Center for Substance Abuse Treatment, Rockville, MD 1995.*

Graphic 78130 Version 9.0

## Clinical Opioid Withdrawal Scale (COWS)

| **Patient's name:**_____ | **Date and time:**___/___/___:_____ |
|---|---|
| **Reason for this assessment:**_____ | |
| **Resting pulse rate:**_____beats/minute<br>Measured after patient is sitting or lying for one minute | **GI upset:** Over last half-hour |
| 0 pulse rate 80 or below<br>1 pulse rate 81 to 100<br>2 pulse rate 101 to 120<br>4 pulse rate greater than 120 | 0 no GI symptoms<br>1 stomach cramps<br>2 nausea or loose stool<br>3 vomiting or diarrhea<br>5 multiple episodes of diarrhea or vomiting |
| **Sweating:** Over past half-hour not accounted for by room temperature or patient activity | **Tremor:** Observation of outstretched hands |
| 0 no report of chills or flushing<br>1 subjective report of chills or flushing<br>2 flushed or observable moistness on face<br>3 beads of sweat on brow or face<br>4 sweat streaming off face | 0 no tremor<br>1 tremor can be felt, but not observed<br>2 slight tremor observable<br>4 gross tremor or muscle twitching |
| **Restlessness:** Observation during assessment | **Yawning:** Observation during assessment |
| 0 able to sit still<br>1 reports difficulty sitting still, but is able to do so<br>3 frequent shifting or extraneous movements of legs/arms<br>5 unable to sit stil l for more than a few seconds | 0 no yawning<br>1 yawning once or twice during assessment<br>2 yawning three or more times during assessment<br>4 yawning several times/minute |
| **Pupil size** | **Anxiety or irritability** |
| 0 pupils pinned or normal size for room light<br>1 pupils possibly larger than normal for room light<br>2 pupils moderately dilated<br>5 pupils so dilated that only the rim of the iris is visible | 0 none<br>1 patient reports increasing irritability or anxiousness<br>2 patient obviously irritable or anxious<br>4 patient so irritable or anxious that participation in the assessment is difficult |
| **Bone or joint aches:** If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored | **Gooseflesh skin** |
| 0 not present<br>1 mild diffuse discomfort<br>2 patient reports severe diffuse aching of joints/muscles<br>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort | 0 skin is smooth<br>3 piloerrection of skin can be felt or hairs standing up on arms<br>5 prominent piloerrection |
| **Runny nose or tearing:** Not accounted for by cold symptoms or allergies | **Total score:**_____<br>The total score is the sum of all 11 items |
| 0 not present<br>1 nasal stuffiness or unusually moist eyes | Initials of person<br>completing assessment:_____ |

| | |
|---|---|
| 2 nose running or tearing<br>4 nose constantly running or tears streaming down cheeks | |

Score: 5 to 12 = mild; 13 to 24 = moderate; 25 to 36 = moderately severe; more than 36 = severe withdrawal.

GI: gastrointestinal.

*Reproduced from: Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003; 35:253.*

Graphic 106994 Version 1.0

**Decision considerations when selecting an opioid agonist medication for a pregnant woman**

| Considerations | Buprenorphine | Methadone |
|---|---|---|
| Patient selection | May be preferable for patients who are new to treatment because it is easier to transfer from buprenorphine to methadone (it can be very difficult to transfer from methadone to buprenorphine), who do not like or want methadone, or who have requested this medication. | May be preferable for patients who do not like or want buprenorphine treatment or who have requested this medication. |
| Care | Includes a prenatal health care professional, parenting classes, and SUD treatment. | Includes a prenatal health care professional, parenting classes, and SUD treatment. |
| Dispensing | May be prescribed in an office setting with weekly or biweekly prescribing/dispensing or provided in an opioid treatment program. | Requires daily visits to a federally certified opioid treatment program; take-home medication is provided for patients meeting specific requirements. |
| Treatment retention | Some studies show treatment dropout is higher than that for methadone. | Some studies show treatment retention is higher than that for buprenorphine. |
| Risk of medication interaction | Few known interactions with other medications; risk of interaction is greatest with CNS depressants and CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, atazanavir). If these medications must be used, the clinic should monitor the patient daily for increased effect of buprenorphine; health care professionals should be aware that the development of sign and symptom varies and depends on a variety of factors.<br>Other agonist/antagonist medications (eg, butorphanol, dezocine, nalbuphine, pentazocine) and full antagonists will result in precipitated withdrawal. | Medications that use CYP450 enzymes are commonly involved in a methadone-medication interaction. Methadone is metabolized primarily by CYP3A4 and CYP2B6. There is evidence that other CYP450 enzymes are also involved including CYP2D6. Known interactions with other medications in pregnant women are detailed elsewhere.[1] If these medications must be used, the clinic should monitor the patient daily for increased or decreased effect of methadone; health care professionals should be aware that the development of sign and symptom varies and depends on a variety of factors.<br>Other agonist/antagonist medications (eg, butorphanol, dezocine, nalbuphine, pentazocine) and full antagonists will result in precipitated withdrawal. |
| Starting dose | 2 to 4 mg sublingually. | 20 to 30 mg orally. |
| Target dose | Daily, 16 mg sublingually or product equivalent to 16 mg sublingually, is the most common dose. The optimal dose will be determined by regular assessment of the individual and her response to treatment. | Daily, 80 to 120 mg orally. The optimal dose will be determined by regular assessment of the individual and her response to treatment. |
| Interval at which dose may be increased | Daily, but dose changes should not be made without patient assessment. | Three days is a common interval in a clinical practice, but dose changes should not be made without patient assessment. |
| Risk of overdose and death | Generally lower risk compared with full opioid agonists; overdose is possible | Generally greater risk of overdose compared with mixed agonist/antagonist |

| | | |
|---|---|---|
| | when combined with other CNS depressants.<br>Continued buprenorphine treatment reduces mortality after release from incarceration.[2]<br>Buprenorphine treatment reduces the risk of death in people dependent on opioids[3] and drug-related mortality in the first four weeks of treatment, a high-risk period.[4] | opioids; overdose is possible when combined with other CNS depressants.<br>Continued methadone treatment reduces mortality after release from incarceration.[2]<br>Methadone significantly reduces the risk of drug-related mortality compared with no treatment.[5]<br>Methadone treatment reduces the risk of death in people dependent on opioids[3] and drug-related mortality in the first four weeks of treatment, a high-risk period.[4] |
| Risk of sedation | Sedation is possible but typically milder than that with full mu opioid agonists. | Sedation is possible and may be greater than that with partial agonist opioids.[6] |
| Ability to fill a prescription at a local pharmacy | Is possible depending on pharmacy availability. | Can be filled in a certified pharmacy to treat pain, but methadone for the treatment of OUD cannot generally be obtained from a pharmacy in the United States. It must be administered or dispensed for treatment of OUD at a certified opioid treatment program. |
| Treatment in a health care professional's office | Health care professionals who request a waiver to prescribe buprenorphine from SAMHSA and receive a unique Drug Enforcement Administration registration number for this purpose may prescribe buprenorphine for the treatment of opioid use disorder in an office-based setting. | May be possible under federal regulation if specific program criteria are fulfilled and relevant state and federal permission is sought. |
| Risk of NAS | Approximately 50% of exposed neonates are treated for NAS; NAS may be milder with buprenorphine compared with full mu opioid agonists such as most opioid analgesics and methadone. | Approximately 50% of exposed neonates are treated for NAS. |
| Time to NAS onset | The AAP recommends monitoring prenatally opioid-exposed neonates for a minimum of four to seven days after delivery.[7] | The AAP recommends monitoring prenatally opioid-exposed neonates for a minimum of four to seven days after delivery.[7] |
| Duration of NAS | Most studies show shorter NAS duration compared with methadone. | Most studies show longer NAS duration compared with buprenorphine. |
| Breastfeeding considerations | Generally safe if the mother is stable and the ABM clinical protocol #21 breastfeeding with SUD guidelines[8] are met. | Generally safe if the mother is stable and the ABM clinical protocol #21 breastfeeding with SUD guidelines[8] are met. |
| Neurodevelopmental outcomes of exposed children | Available research suggests there is not a linear cause and effect relationship between prenatal buprenorphine exposure and developmental problems when compared with other opioids; the research base is limited. | Available research suggests there is not a linear cause and effect relationship between prenatal methadone exposure and developmental problems when compared with other opioids; the research base is limited. |

SUD: substance use disorder; CNS: central nervous system; OUD: opioid use disorder; SAMHSA: Substance Abuse and Mental Health Services Administration; NAS: neonatal abstinence syndrome; AAP: American Academy of Pediatrics; AMB: Academy of Breastfeeding Medicine.

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## Contributor Disclosures

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