

# Chronic Opioid Use During Pregnancy: Maternal and Fetal Implications

Todd J. Stanhope, MD, Lisa A. Gill, MD, Carl Rose, MD\*

## KEYWORDS

- Opioid • Narcotic • Pregnancy • Methadone • Buprenorphine

## KEY POINTS

- A collaborative, multidisciplinary care approach is essential for pregnancies complicated by chronic narcotic use.
- Management of opioid dependence with either methadone or buprenorphine is appropriate during pregnancy and breastfeeding.
- Detoxification with careful observation is reasonable during pregnancy in appropriately selected patients and is best accomplished during the second or early third trimester.
- Usage of prescription monitoring programs or the evolving Risk Evaluation and Mitigation Strategy (REMS) program may be beneficial in prevention of inappropriate prescribing or diversion.

## INTRODUCTION

Concern regarding the use and abuse of both prescription and illicit opioid medications has been a growing medical and societal concern within the United States during the past decade. Since the early 2000s, prescriptions for the opioid, hydrocodone, have exceeded those for either antibiotic or antihypertensive medications.<sup>1</sup> Similar to many chronic medical conditions, this phenomenon is proportionally represented in the pregnant population, with attendant implications for not only the mother but also the unborn child.<sup>2</sup> This article reviews the issues related to prescription and illicit opiate use during pregnancy and proposes strategies for antepartum, intrapartum, and postpartum management.

## CLASSIFICATIONS

Opioid medications are defined by the Food and Drug Administration (FDA) as synthetic alkaloid derivatives of the chemical opium and are classified by the Drug

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Conflicts of Interest: None.

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mayo Clinic, 200 First Street SW, Rochester, MN 55902, USA

\* Corresponding author.

E-mail address: [rose.carl@mayo.edu](mailto:rose.carl@mayo.edu)

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Enforcement Agency (DEA) as schedule II, III, or IV contingent on clinical efficacy and abuse potential (**Table 1**).<sup>3,4</sup> Specialized prescription forms (triplicates) are required in most states for schedule II medications. For obstetric purposes, opioid compounds are classified as either category B or C by the FDA for use during pregnancy, with no confirmed human teratogenic effects reported. The term, *narcotic*, refers to induction of drowsiness or sleep but is also used synonymously in common literature to refer to opioid-category medications from a generic perspective. Specifically, the descriptor, *opiate*, refers to compounds derived directly from natural sources (opium and endogenous opioids), although the words are often used interchangeably.

### MECHANISM OF ACTION

All opioids exert their effects primarily through binding to 1 or more of 3 opioid receptors ( $\mu$ ,  $\kappa$ , and  $\Delta$ ), which are widely distributed throughout the body, including the vascular, cardiac, pulmonary, gastrointestinal, and immune systems. The analgesic effect occurs through activation of receptors found in both central and peripheral nervous systems, whereas side effects, such as respiratory depression and decreased

**Table 1**  
Common opioid medications

Medication	DEA Schedule	FDA Category	Duration of Action (h)
Hydromorphone (Dilaudid)	II	C	3–4
Hydrocodone (Lorcet, Vicodin)	II	C	4–8
Oxycodone (OxyContin, Roxicodone)	II	B	3–6
Meperidine (Demerol)	II	C	2–4
Codeine	II	C	4–6
Morphine (Duramorph, MS Contin)	II	C	4
Tramadol (Ultram)	IV varies by state	C	9
Methadone (Dolophine)	II	C	4–8 Single doses 22–48 Repeat doses
Heroin (not commercially available)	I	Not assigned	3–4
Buprenorphine (Buprenex, Subutex) (combined opioid agonist/antagonist)	III	C	$\geq 6$
Naloxone (Narcan) (opioid antagonist)	Not assigned	C	0.5–2

DEA schedules (summarized)<sup>60</sup>: I, no currently accepted medical use and a high potential for abuse; II, high potential for abuse, although less than schedule I—drugs are considered dangerous; III, moderate to low potential for dependence; IV, low potential for abuse and low risk of dependence; and V, lower potential for abuse than schedule IV and contain limited dose of narcotics.

FDA medication pregnancy categories (summarized)<sup>61</sup>: A, adequate studies have failed to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters); B, animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women; C, animal studies have demonstrated adverse effects on the fetus and there are no adequate controlled studies in humans—potential benefit may outweigh potential risks for use in pregnant women; D, there is positive evidence of human fetal risk, but the potential benefits from use in pregnant women may be acceptable despite the risk; and X, studies in animals or human have demonstrated fetal abnormalities or there is evidence of fetal risk, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

*Data from* DEA Drug Scheduling. Retrieved from the United States Drug Enforcement Agency Web site: <http://www.justice.gov/dea/druginfo/ds.shtml>. Accessed December 17, 2012.

intestinal motility, result from activation of peripheral receptors. The specific formulations differ in agonist or antagonist function as well as duration of action.

Pure opioid agonists activate all receptor types and are commonly used both clinically and illicitly for their analgesic and euphoric effects. Conversely, mixed agonist-antagonist formulations interact differently with each receptor type and were designed to have decreased addictive potential relative to pure agonists. This combination results in a ceiling effect on the maximum analgesia and euphoria experienced by the user, making this class favorable for treating opioid dependence. Opioid antagonists, such as naloxone and its analog naltrexone, function by competitively binding to the  $\mu$  receptor to inhibit effects at a cellular level and can be used as reversal agents when opioid intoxication is suspected.<sup>5</sup>

Opioid receptor activation may have other effects, such as sedation, pruritus, nausea, and vomiting. Chronic use may lead to hyperalgesia as tachyphylaxis or tolerance develops, requiring escalating doses to provide similar desired analgesic effects.<sup>6</sup> Because individual response to particular medications may vary, the practice of opioid rotation (also known as opioid switching), or the transitioning from one formulation to another, may be of benefit in patients suffering from refractory side effects or inadequate analgesia with one specific drug. Similarly, the use of multiple opioid medications simultaneously (combined therapy) has been suggested to improve synergistic efficacy as well.

## PRESCRIPTION MEDICATIONS

Common prescription medications include either pure opioid medications or formulations of an opioid medication combined with a complementary nonopiod analgesic. Such compounded medications usually contain acetaminophen or a nonsteroidal anti-inflammatory drug, such as ibuprofen, for additional analgesia. Most are dispensed in oral or transdermal forms, with intramuscular or intravenous preparations reserved for inpatient settings. Opioid compounds also constitute the primary active ingredient found in several medications prescribed for nonanalgesic indications, including cough suppressants and syrups.

### ***Prescribing Practices***

To date, no specific data exist suggesting that alteration of standard prescribing practices is required during pregnancy. Some states do not permit verbal pharmacy orders or facsimile transmission of prescriptions for controlled substances due to concern for diversion, instead mandating that original prescriptions be submitted. Unfortunately, the online pharmaceutical industry is only minimally regulated, particularly for locations outside of the United States. Consequently, so-called nonprescription Web sites illegitimately market opioid and other controlled substances in a semianonymous manner without requiring prescriptions.<sup>7</sup> In 2013, 46 states have operational prescription monitoring programs, with intent to reduce drug diversion practices; however, existing data attesting to their effectiveness remain conflicting.<sup>8</sup> An analysis performed in 2011 showed no difference in opioid mortality when comparing states with tracking programs and those without.<sup>9</sup> From the current data, it is unclear whether these programs alter prescribing practices and, if so, the resulting clinical impact.

In most states, however, where prescription monitoring programs are available, they are used by less than 25% of physicians prescribing narcotic medications.<sup>10</sup> In addition to low usage of the systems where they are available, some states do not permit direct access by the prescribing physicians, instead shifting the responsibility to law enforcement. Additionally, the types of medications that are reported to these

databases vary from state to state, with some states tracking only schedule II medications and others tracking schedule II–IV medications.

### ***Methadone***

Methadone is a synthetic opioid originally developed in the 1930s and first manufactured in the United States in 1947. Most commonly prescribed for the treatment of heroin addiction, it has also been used in the management of chronic pain syndromes and more recently for prescription opioid abuse.<sup>11</sup> Methadone binds to the  $\mu$ -opioid receptor as a competitive agonist and also competitively inhibits binding of the neurotransmitter glutamate to the *N*-methyl D-aspartate receptor within the central nervous system, mitigating some of the physiologic symptoms associated with opioid withdrawal. The elimination half-life of methadone (8–59 hours) is much longer than its analgesic effect (4–8 hours). Classified as a category C medication for use during pregnancy due to concerns for low birthweight and potential teratogenicity, methadone treatment has nevertheless been demonstrated to reduce actions associated with illicit substance use (drug-seeking behavior and prostitution) and provide a more pharmacologically stable fetal environment.<sup>12</sup>

Methadone therapy may be started during any trimester of pregnancy in either an inpatient or outpatient setting. Candidates should undergo standard medical examination, with particular attention to sonographic determination of fetal gestational age, screening for illicit drug use, and serologic studies for infectious diseases (HIV, hepatitis B, and hepatitis C). During the first 24 hours, an initial dose is administered followed by successive lower doses based on maternal symptoms (Box 1). During the second day, the cumulative total dose from the first day is administered, with further dosing as required until the patient remains free of withdrawal symptoms for a 24-hour interval (stabilization dose). Typical stabilization doses during pregnancy are 80 mg to 120 mg daily, whereas less than 60 mg daily is likely ineffective. Due to enhanced metabolism during pregnancy, twice-daily or thrice-daily administration may be beneficial in select circumstances.<sup>13,14</sup> Split-dosing regimens also seem to have lessened effects on fetal assessments and may be particularly effective for patients on higher doses who continue to experience symptomatology.<sup>15</sup> Serum trough levels have been described if confirmation of physiologic withdrawal is required.<sup>16</sup> Supplemental opioid analgesics should be avoided if at all possible. Treatment with diacetylmorphine (heroin-assisted treatment) has been described in fewer than 10 patients to date, ostensibly to reduce ongoing illicit substance use, without adverse outcome.<sup>17</sup>

For patients who conceive while enrolled in methadone treatment programs, further titration of dose is usually deferred until after delivery but otherwise follows similar management principles. Surveillance toxicology screening at each prenatal visit is suggested (and may be a legal requirement) to detect concurrent polysubstance abuse. Serial sonography to determine interval fetal growth seems warranted due to a possible increased risk of intrauterine growth restriction.<sup>18</sup> The antepartum dose is usually continued intrapartum and immediately postpartum, although some investigators have suggested decreasing the maintenance dose by 20% to 40% after delivery.<sup>19</sup> Breastfeeding is considered permissible by the American Academy of Pediatrics.<sup>20</sup>

### ***Buprenorphine***

Buprenorphine is a partial opioid agonist approved for treatment of opioid dependency by the FDA in 2002. Exclusively buprenorphine (Subutex) formulations are preferred over the buprenorphine/naloxone combination (Suboxone) during

**Box 1****Methadone and buprenorphine prescribing regimens***Methadone regimens*

## Initiation (typically as an inpatient)

- Day #1: methadone 20–30 mg loading dose in morning, then 5–10 mg every 3–6 hours PRN for withdrawal symptoms.
- Day #2: cumulative total from day #1 administered as single morning dose with 5–10 mg doses every 3–6 hours as needed for withdrawal symptoms. Typically increase by 10–20 mg per day.
- Continue to escalate dose until no withdrawal symptoms for  $\geq 24$  hours (stabilization).

## Maintenance

- Continue daily dose previously prescribed.
- Increase dose by 5–10 mg per day every 3–7 days (as required) to prevent withdrawal symptoms. Typical daily dose is 80–120 mg. Doses less than 60 mg are associated with increased relapse.
- Daily dose may be split into 8-h or 12-h intervals (if feasible) for refractory symptoms or during pregnancy.

*Buprenorphine regimens*

## Initiation

- Must be abstinent from opioids for more than 24 hours or risk of withdrawal symptoms.
- Day #1: start 4 mg and observe. If withdrawal symptoms, may repeat dose for total 8 mg.
- Day #2: give prior day dose and observe. May increase by 4 mg increments to maximum 16 mg.
- Titrate by 4–8 mg increments every few days until symptoms resolved (maximum dose 32 mg).

## Maintenance

- Continue daily dose as previously prescribed.
- Consider splitting daily dose into 6-h intervals during labor.

Opioid dependence may be managed during pregnancy and lactation with methadone or buprenorphine. Patient response to treatment is variable, so the dosages should be titrated to manage withdrawal symptoms. Due to the long half-life of methadone, incremental changes to maintenance should be made slowly.

pregnancy because the latter may precipitate withdrawal symptoms. Although the incidence of neonatal abstinence syndrome (NAS) is reportedly lower in patients treated with buprenorphine, current data do not suggest other specific benefits compared with methadone therapy.<sup>21,22</sup> Typical daily doses range between 8 mg and 16 mg, with a maximum dose of 32 mg (see **Box 1**). Similar to methadone, daily therapy is continued intrapartum, although the total daily dose may be divided to every 6 hours for enhanced analgesic effect. Postpartum, if greater than 48 hours of supplemental opioid therapy is anticipated (as with cesarean delivery or other complex surgical procedure), buprenorphine should be discontinued and therapy reinstated once acute analgesic requirements have diminished.<sup>23</sup> Breastfeeding seems safe and does not increase risk of neonatal dependence, although data are limited.<sup>24</sup>

## DETOXIFICATION DURING PREGNANCY

Although early reports suggested increased risks of spontaneous abortion, preterm delivery, and intrauterine fetal demise associated with opioid detoxification, the most comprehensive series suggests no increased risk of pregnancy complications.<sup>25</sup> Dose reduction and discontinuation of opiates may be attempted in motivated patients to reduce the risk of NAS, optimally during the second or early third trimester. Preexisting fetal growth restriction and oligohydramnios are considered relative contraindications. Choice of agent remains with clinicians because buprenorphine and methadone are both appropriate for use in pregnancy and have equivalent rates of subsequent NAS. In a multicenter randomized controlled trial of 175 pregnant women with opioid dependency, buprenorphine was associated with shorter duration of hospital stay (4.1 vs 9.9 days), decreased antepartum morphine requirements, and shorter neonatal hospital stay (10.0 vs 17.5 days) compared with methadone therapy. Discontinuation of therapy was more common, however, with buprenorphine (33%) than with methadone (18%).<sup>11</sup> Consequently, either medication is appropriate depending on physician comfort and the clinical scenario.

For methadone-naïve patients, a stabilization dose may be achieved followed by dose reductions of 20% every 72 hours. For patients on maintenance methadone therapy, protocols have described reductions of 2 mg to 5 mg every 6 to 16 days, with inpatient admission for taper and discontinuation at daily doses of less than or equal to 20 mg.<sup>26</sup> Unfortunately, the recidivism rate is approximately 40%, tempering the practical applicability of this approach. Only limited protocols for buprenorphine detoxification during pregnancy have been described and do not report adverse maternal or fetal outcomes.<sup>27,28</sup>

## ILICIT SUBSTANCES

Nonmedical use of prescription medications represents the second most common category of illicit drug use after marijuana, with opioid medications representing the majority. Of pregnant women aged 15 to 44, an average of 5% admitted to use of illicit substances in a national survey conducted in 2010–2011. Pregnant women aged 15 to 17 represented the highest risk group, with 20.9% indicating usage.<sup>29</sup> Heroin (diacetylmorphine) is the most commonly abused nonprescription opiate and rates of use, dependence, and death in persons 12 years and older have steadily increased over the past decade. Heroin may be administered nasally, intravenously, or via inhalation and is often compounded or adulterated with other substances, including cocaine, strychnine, quinine, and talc.<sup>30</sup>

The American Congress of Obstetricians and Gynecologists recommends routine screening for substance abuse in pregnancy.<sup>6</sup> Risk factors include adolescent age, single marital status, late or irregular prenatal care, lower level of education completed, history of high-risk sexual behavior, personal or family history of drug dependence, poor weight gain, poor dentition, and history of a mental health disorder. Physical examination may reveal skin lesions, such as track marks along superficial veins, abscesses, or cellulitis. Due to the risk of concomitant infectious disease, serologic testing for HIV, hepatitis B, and hepatitis C should be performed at the initial prenatal visit and repeated during the third trimester. Withdrawal of opioids in dependent patients is generally contraindicated during pregnancy due to risks of withdrawal symptoms and relapse as well as fetal distress or demise.<sup>7,31</sup> Rather, opioid-assisted therapy in the setting of an addiction treatment program is preferable to maintain continuity of care and reduce high-risk behaviors. A medically supervised withdrawal

conducted by an experienced provider may be appropriate when a methadone or buprenorphine program is unavailable or if a patient refuses this intervention.

## **OBSTETRIC COMPLICATIONS**

Adverse perinatal outcomes resulting from prescription or illicit substance use comprise a spectrum of maternal and fetal complications through both direct toxicity and engagement in activities and lifestyles related to drug procurement (infectious diseases and trauma).<sup>32</sup> Described specific obstetric complications include preterm delivery, abruptio placenta, fetal growth restriction, and intrauterine fetal demise.<sup>7</sup> Opioid medications have not traditionally been considered to increase the risk of fetal birth defects, although this has been questioned in a recent review that suggests an increased risk of cardiac malformations.<sup>33,34</sup> Because many patients using illicit substances abuse multiple drugs in varying degrees, isolating the effects of any single drug is often impractical.<sup>35</sup> Although rare, the sharing of contaminated needles for injection can lead to alloimmunization in Rh-negative individuals.

## **GUIDELINES FOR PREGNANCY MANAGEMENT**

Although recognizing that a single strategy may not be applicable to all circumstances and little formal evidence exists to guide various aspects of prenatal care, the authors suggest the following multidisciplinary approach, as practiced in their institution, to management of pregnancy complicated by opioid dependence:

### ***Antepartum***

1. At time of initiation of prenatal care, obtain routine prenatal laboratory studies; hepatitis C, gonorrhea, and chlamydia screening; serum/urine toxicology studies; and formal sonography to confirm gestational age.
2. For patients with history or current illicit substance use, consider repeat toxicology screening at each prenatal appointment and repeat HIV, syphilis and gonorrhea, and chlamydial screening at 36 weeks or sooner as clinically indicated.
3. Consultations with Social Work, Psychiatry and Addiction Counseling may be obtained as indicated. Notification of legal authorities is required in some states according to child protection statutes.<sup>36</sup>
4. All prescriptions should be coordinated through a single provider (or practice group) to avoid multiple providers prescribing simultaneously and to limit the potential for medication diversion.
5. If available, online state prescription monitoring programs should be reviewed periodically.
6. Early patient education regarding the potential fetal/neonatal effects of chronic opioid use is critical, with discontinuation or limitation of use as is feasible. Establish clear limits early in gestation in regard to prescriptions provided. As a general rule, the authors' institution has not engaged patients in formal prescribing contracts during pregnancy; however, this may be an option in particularly challenging situations. Rotation of medications may be required in selected circumstances.
7. Consider referral to a pain management or pain rehabilitation provider (if locally available).
8. Perform serial sonography on a monthly basis from 24 weeks' gestation to confirm interval fetal growth.
9. Some authors recommend weekly antenatal surveillance beginning at 32 weeks due to increased risk of fetal demise.

10. Although chronic opioid use has been described to reduce fetal heart rate accelerations and breathing movement on biophysical profile testing, in clinical practice this is not a consistent effect. Methadone has been demonstrated to reduce fetal heart rate with decreased variability and less frequent accelerations.<sup>37,38</sup>
11. Preparation for delivery may be facilitated by Neonatology/Pediatric consultation in the third trimester to discuss implications for nursery care and criteria for infant discharge from the hospital.
12. The provider must recognize that fear of legal revocation of parental custody may preclude some patients from obtaining prenatal care, particularly if they are presently engaged in illicit substance use or active prescription drug diversion.

#### ***Intrapartum***

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1. Notify neonatology/pediatrics and anesthesiology at time of admission.
2. Continuation of the previous antepartum medication regimen is usually feasible during labor. For patients receiving methadone or buprenorphine, confirmation of current dosage with dispensing clinic is suggested.
3. Some patients, particularly those engaged in illicit substance use, may exhibit hyperalgesia to labor discomfort and require substantial doses of intravenous analgesics for relief. Neither methadone nor buprenorphine is typically exclusively sufficient for intrapartum analgesia.
4. Similar to antepartum fetal assessment, although alterations in fetal heart rate patterns have been described, parameters for intrapartum fetal assessment should follow standard obstetric guidelines.<sup>39</sup>

#### ***Postpartum***

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1. Similar to the intrapartum interval, higher doses of analgesic medications may be required postpartum to achieve patient comfort, particularly after cesarean delivery.
2. Anticipated incidence of NAS is approximately 6% to 71% for patients receiving chronic opioid prescriptions.<sup>40</sup> Naloxone is generally avoided in the treatment of neonatal respiratory depression due to concern of precipitating opioid withdrawal seizures.<sup>41</sup>
3. Lactation is permissible in the absence of standard obstetric contraindications (HIV, active tuberculosis, and so forth)
4. Before maternal discharge, a clear plan should be formulated for scheduled subsequent return visits and anticipated postpartum analgesic requirements. If a patient is typically prescribed maintenance opioid therapy from a nonobstetric provider, transitions in prescribing should be discussed in advance with the patient and all involved providers.
5. Postpartum contraceptive options should be discussed.

#### **NEONATAL ABSTINENCE SYNDROME**

NAS, also termed neonatal opioid withdrawal, is generally defined as a constellation of physiologic symptoms due to cessation of opioid exposure after interruption of the fetoplacental circulation at time of delivery. Onset may be related to maternal medication elimination half-life but typically occurs within 1 to 10 days of delivery. Symptoms can include dehydration, excessive crying, diarrhea, increased muscle tone, hyperreflexia, fever, congestion, diaphoresis, irritability, difficulty sleeping, or seizures.<sup>42</sup> These effects seem most pronounced in preterm infants or after maternal methadone

or heroin use, with some investigators describing rates as high as 71%. Paradoxically, data regarding the risk of NAS do not consistently correlate with methadone dosage.<sup>43,44</sup> Duration of inpatient neonatal observation should be dependent on the specific maternal opioid used during pregnancy.<sup>45</sup>

Minimal data currently exist describing the frequency of NAS occurring in infants born to mothers receiving chronic prescription opioid therapy. A recent review of discharge documentation suggests, however, that a 3-fold increase in NAS has occurred in the United States over the past decade.<sup>46</sup> A recent retrospective investigation from Kellogg and colleagues<sup>40</sup> found that 0.6% of patients were prescribed opioid medications for the duration of pregnancy, with a 6% incidence of NAS. Neonatal outcomes were not stratified by specific maternal dosage. A recent report also suggested 6% of Norwegian pregnant patients are prescribed opioids before conception, during pregnancy, or after delivery, with the majority for short-term indications.<sup>47</sup>

Confirmatory testing of neonatal urine, hair, or meconium samples may be performed but because results are usually not rapidly available, presumptive treatment should be initiated in the interim. Several objective scoring systems have been developed to identify infants requiring treatment and to guide escalation of therapy. Treatment of NAS comprises of avoidance of excess stimulation of the newborn, frequent low-volume/high-calorie feedings, and institution of morphine or methadone therapy contingent on symptoms score (**Table 2**). Phenobarbital may be effective in refractory cases or for infants exposed to multiple illicit substances. Once neonatal condition is stabilized, medication doses are gradually incremental decreased (weaning) over the following days to weeks.

**Table 2**  
**Modified Finnegan neonatal abstinence scoring tool**

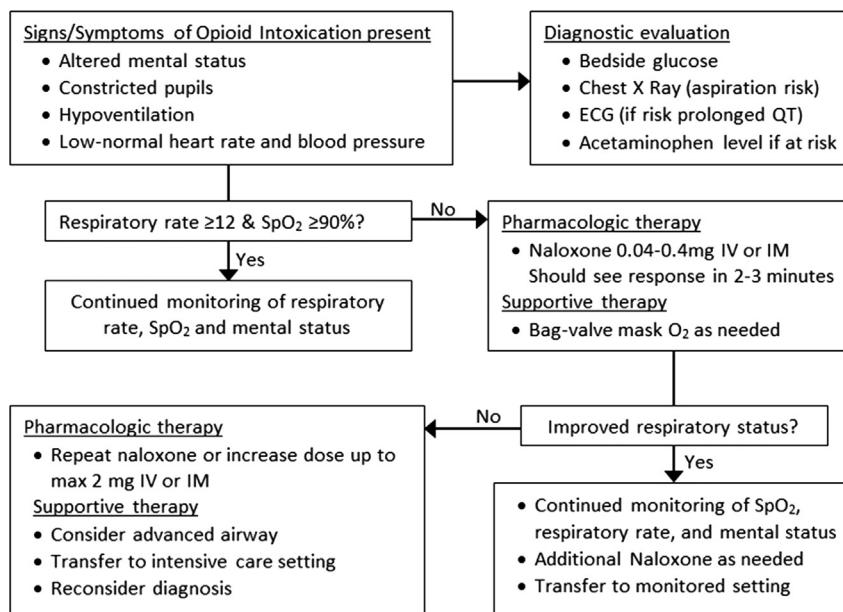
Neonatal Abstinence Scoring System			
Symptom	Score	Symptom	Score
Continuous high pitched (or other) cry	2	Sweating	1
Continuous high pitched (or other) cry	3	Fever 100.4°–101°F (38°–38.3°C)	1
Sleeps <1 h after feeding	3	Fever >101°F (38.3°C)	2
Sleeps <2 h after feeding	2	Frequent yawning (>3–4 times/interval)	1
Sleeps <3 h after feeding	1	Mottling	1
Hyperactive Moro reflex	2	Nasal stuffiness	1
Markedly hyperactive Moro reflex	3	Sneezing (>3–4 times/interval)	1
Mild tremors disturbed	1	Nasal flaring	2
Moderate–severe tremors disturbed	2	Respiratory rate >60/min	1
Mild tremors undisturbed	3	Respiratory rate >60/min with retractions	2
Moderate–severe tremors undisturbed	4	Excessive sucking	1
Increased muscle tone	2	Poor feeding	2
Excoriation (specific area)	1	Regurgitation	2
Myoclonic jerks	3	Projectile vomiting	3
Generalized convulsions	5	Loose stools	2
		Watery stools	3

Modified Finnegan score obtained at 2-hour intervals after delivery. A score  $\geq 8$  on 3 or more consecutive occasions generally requires pharmacologic intervention. Blue, central nervous system disturbances; yellow, metabolic/vasomotor/respiratory disturbances; and green, gastrointestinal disturbances.

Developmental outcomes for exposed infants are challenging to definitively categorize, with some epidemiologic studies showing an increased incidence of neurobehavioral issues later in childhood and others demonstrating no differences from age-matched cohorts.<sup>48</sup> A recent report comparing imaging studies in methadone-exposed neonates suggested delayed maturation of cortical neural tracts.<sup>49</sup> Quantification of individual substance effects is difficult to ascertain due to confounding environmental and social factors, which may ultimately play a larger role in determining outcomes.<sup>50</sup>

## MANAGEMENT OF ACUTE OPIOID OVERDOSE

Presenting signs of opioid overdose include lethargy, confusion, pupillary constriction, decreased respiratory rate, and, in extreme cases, obtundation or respiratory arrest. Initial efforts should focus on standard cardiopulmonary resuscitation, followed by an initial dose of intravenous naloxone to restore respiratory function.<sup>51</sup> Basic laboratory studies (including serum glucose) should be obtained with ECG, chest radiography, and cranial imaging based on individual clinical scenario (Fig. 1).<sup>52,53</sup> Some reports have suggested reversal of buprenorphine overdose may require higher doses of naloxone.<sup>54</sup> Once maternal condition has been stabilized, the patient should be transported to an appropriate obstetric unit for fetal assessment and continued observation.



**Naloxone use:** Goal of treatment is improved respirations, not improved mental status. Excess dose may result in withdrawal symptoms. Duration of action is 45-70 minutes, whereas most ingested opioids last much longer (often 24-72 hours). Repeat doses will likely be required. Continuous intravenous infusion may also be used in such cases.

**Fig. 1.** Management of acute opioid intoxication. Keys to management of opioid intoxication include supportive therapy and opioid agonists to improve respiratory status.

## PREVENTION OF OPIOID ABUSE

Several strategies have been proposed for the prevention of prescription and nonprescription opioid abuse<sup>55–57</sup>:

1. Limitation of prescription refills through specific insurance coverage limitations or restrictions and state prescription monitoring oversight programs to track pharmacy dispensing
2. Creation and enforcement of regulations against doctor shopping or distribution of narcotic medications without adequate medical evaluation
3. Mandatory education of health care providers on evidence-based guidelines regarding appropriate and effective prescribing practices
4. Continuity of care with a single provider

In 2011 the FDA charged all manufacturers of opiate medications to develop and implement a REMS program to educate health care providers regarding the safe prescribing of extended-release/long-acting formulations, with the final protocol released in July 2012.<sup>58,59</sup>

## SUMMARY

Prescription and nonprescription chronic opioid abuse represents a growing problem in the United States that will likely increase during the next several years. Strategies for management during pregnancy include discontinuation of narcotic medications with careful observation for withdrawal symptoms, limitation of prescriptions, and medical therapy with methadone or buprenorphine therapy reserved for patients with addiction or dependence—either agent is appropriate for use during pregnancy and breastfeeding, although more data presently exist for methadone treatment. NAS may occur with maternal use of any opioid medication but seems most common with methadone or illicit substance use. Given these multiple challenges, referrals to providers with experience in addiction management, social work, chronic pain, and pediatrics should be made during the antepartum course, with plans for delivery at a facility with availability of adequate resources and staff. Use of prescription monitoring programs or the evolving REMS program may be beneficial in prevention of inappropriate prescribing or diversion, although efforts should be made to create a nonjudgmental environment to reduce risk-taking behaviors and recidivism. Maintaining regular care for opioid-dependent pregnant patients with this multidisciplinary team approach will aid in achieving optimal outcomes for both mothers and their babies in this otherwise challenging scenario.

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