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# Treatment of opioid-dependent pregnant women: Clinical and research issues

Hendree E. Jones, (Ph.D.)[a,*], Peter R. Martin, (M.D.)[b], Sarah H. Heil, (Ph.D.)[c], Karol Kaltenbach, (Ph.D.)[d], Peter Selby, (M.B.B.S.)[e], Mara G. Coyle, (M.D.)[f], Susan M. Stine, (M.D., Ph.D.)[g], Kevin E. O'Grady, (Ph.D.)[h], Amelia M. Arria, (Ph.D.)[h], Gabriele Fischer, (M.D.)[i]

[a]*Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[b]*Department of Psychiatry, Vanderbilt University, Nashville, TN, USA*
[c]*Department of Psychiatry and Psychology, University of Vermont, Burlington, VT, USA*
[d]*Department of Pediatrics, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA*
[e]*Departments of Family and Community Medicine, Psychiatry and Public Health Sciences, University of Toronto, Toronto, Ontario, Canada*
[f]*Department of Pediatrics, The Warren Alpert Medical School of Brown University, Providence, RI, USA*
[g]*Department of Psychiatry and Behavior Neurosciences, Wayne State University, Detroit, MI, USA*
[h]*Center for Substance Abuse Research, University of Maryland, College Park, MD, USA*
[i]*Department of Psychiatry, Medical University of Vienna, Vienna, Austria*

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**Abstract**

This article addresses common questions that clinicians face when treating pregnant women with opioid dependence. Guidance, based on both research evidence and the collective clinical experience of the authors, which include investigators in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, is provided to aid clinical decision making. The MOTHER project is a double-blind, double-dummy, flexible-dosing, parallel-group clinical trial examining the comparative safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence in pregnant women and their neonates. The article begins with a discussion of appropriate assessment during pregnancy and then addresses clinical management stages including maintenance medication selection, induction, and stabilization; opioid agonist medication management before, during, and after delivery; pain management; breast-feeding; and transfer to aftercare. Lastly, other important clinical issues including managing co-occurring psychiatric disorders and medication interactions are discussed. 

*Keywords:* Pregnancy; Substance abuse; Pharmacologic treatment; Opioid dependence; Methadone; Buprenorphine

## 1. Introduction

### *1.1. Rationale for treating opioid-dependent pregnant patients with agonist medication*

Opioid-dependent pregnant women face tremendous stigma from their family, social networks, and society. Health care providers can mitigate this source of stress by directly addressing their patient's fears, guilt, and treatment resistance. Historically, there has been considerable debate about the optimal management of opioid-dependent pregnant women, given the potential risks of medications to the fetus. A particular concern has been the occurrence of neonatal withdrawal. On the basis of these concerns, some opioid-dependent pregnant women are treated inadequately, with either no medication or subtherapeutic levels of medication, to reduce the exposure and risk for physical dependence in the fetus. However, the benefits of methadone are well

* Corresponding author. Cornerstone/JHBMC, Mason F. Lord Building, E353, 4940 Eastern Avenue, Baltimore, MD 21224, USA.
*E-mail address:* hejones@jhmi.edu (H.E. Jones).

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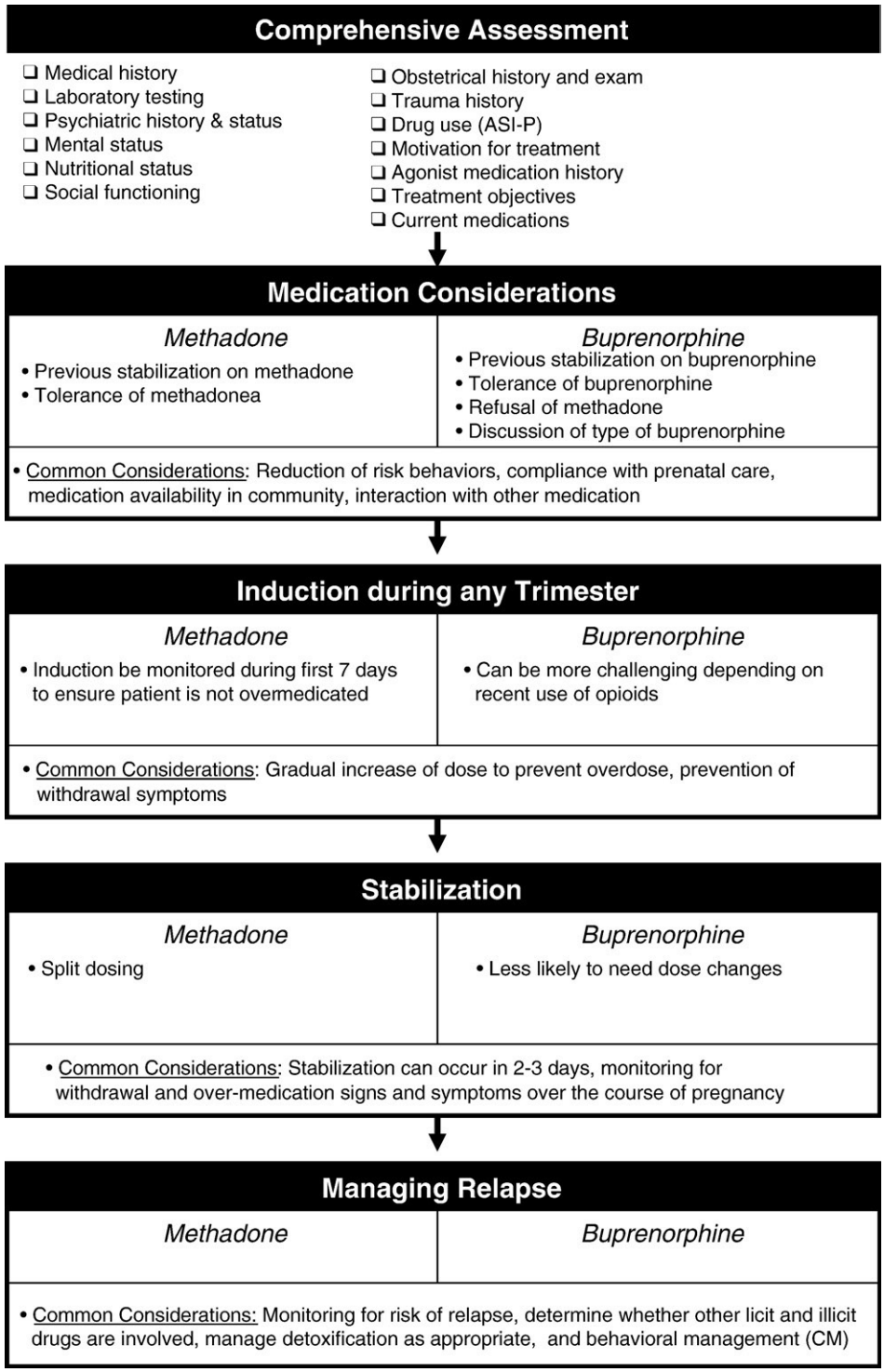


Fig. 1. Considerations in the clinical management of the opioid-dependent pregnant woman. Considerations specific to methadone and buprenorphine are listed on the left and right, respectively, of each module. Considerations that apply to both medications are listed in the shared panel at the bottom of each module.

documented. Although not formally approved by the U.S. Food and Drug Administration (FDA) for treatment during pregnancy, methadone has been the current recommended standard of care for opioid-dependent pregnant women since the early 1990s (National Institutes of Health Consensus Development Panel, 1998).

In pregnant patients, methadone substantially minimizes the peak and trough in maternal serum opioid levels that typically occur with repeated use of short-acting opioids (i.e., heroin), thereby reducing the harm the fetus encounters as a result of repeated intoxication and withdrawal (e.g., Kaltenbach, Berghella, & Finnegan, 1998). Compared with other approaches to

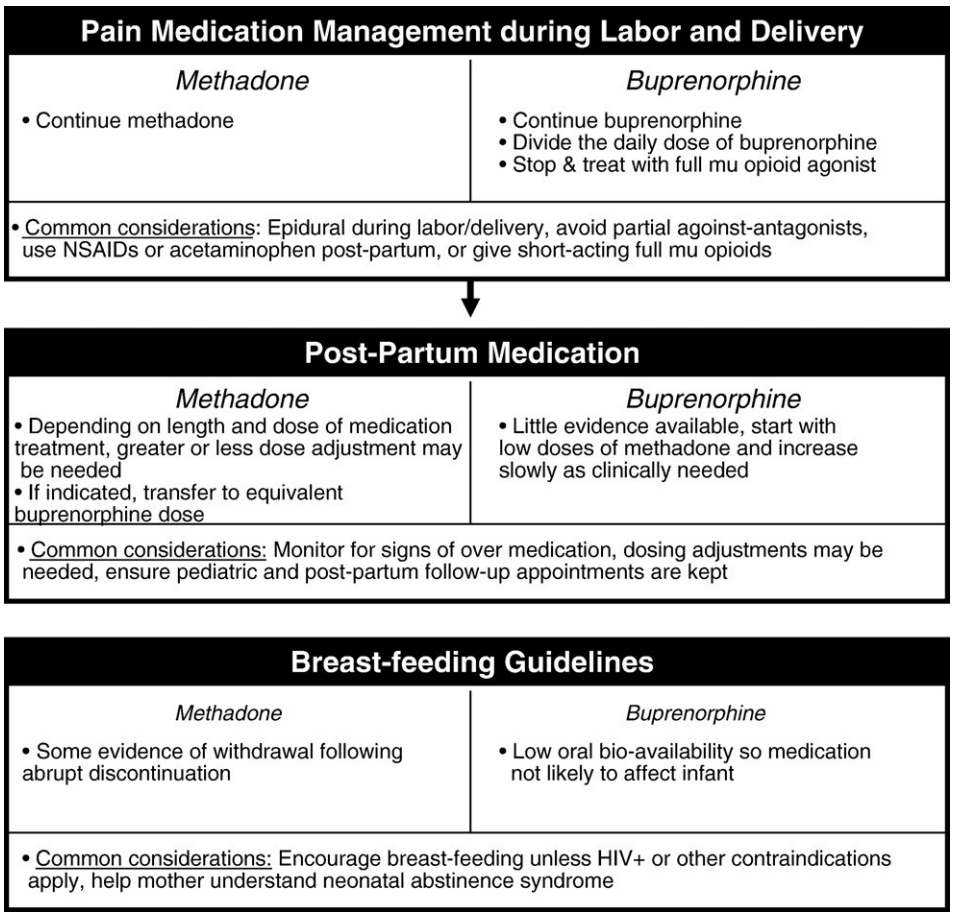


Fig. 1 (*continued*)

treatment of opioid dependence available at the time, methadone maintenance was the most cost-effective, producing the greatest reductions in heroin use, criminal activity, and days of hospitalizations (Gerstein, 1992). Thus, the benefits of methadone are clear. Methadone maintenance relative to medication-assisted withdrawal provides superior relapse prevention, reduces fetal exposure to illicit drug use and other maternal risk behaviors, improves adherence with obstetrical care, and enhances neonatal outcomes (e.g., heavier birth weight; see Kaltenbach et al., 1998 for a review of this topic).

After the approval of buprenorphine use in treatment of opioid dependence in nonpregnant populations, women have conceived while on this medication—and other women have entered treatment requesting buprenorphine due to its unique pharmacology and its availability in the private practitioner setting. Thus, there is new interest in better understanding the use of opioid maintenance medications during pregnancy and in evaluating the suitability of buprenorphine to be approved by the FDA for use during pregnancy.

### *1.2. Risk–Benefit assessment*

In spite of the strong evidence supporting the use of methadone in pregnancy, methadone is not without risk or side effects. Neonatal withdrawal after methadone exposure is often of longer duration than that after heroin exposure (Wilson, Desmond, & Wait, 1981). Methadone administration appears to alter fetal activity and heart rate (Jansson, Dipietro, & Elko, 2005; Ramirez-Cacho, Flores, Schrader, McKay, & Rayburn, 2006). However, as described above, the benefits that methadone provides within a comprehensive care setting to this patient population far outweigh the potential risks of treatment.

Although buprenorphine is only approved for the treatment of opioid dependence in nonpregnant populations, it is being prescribed frequently to opioid-dependent pregnant patients. Thus, patients should be informed that studies regarding safety and efficacy of prenatal exposure to buprenorphine are currently in progress, that the data regarding the prenatal effects of buprenorphine are incomplete as compared with those of methadone, and that the recommendations regarding buprenorphine during pregnancy are necessarily in flux. Currently available data do not indicate that buprenorphine treatment during pregnancy is associated with greater risk to the mother or embryo or fetus than treatment with methadone (Fischer et al., 2006; Jones et al., 2005; LeJeune et al., 2006). However, patient management with the use of buprenorphine presents unique

challenges and potential benefits compared with those encountered with methadone, the accepted standard of care. Given the different pharmacology of the two medications, methadone and buprenorphine cannot be used interchangeably, and methadone-maintained patients are usually not always good candidates for buprenorphine.

### 1.3. Objectives of this article

Evidence-based guidance is needed to optimize the care of the thousands of pregnant women each year who are prescribed either methadone or buprenorphine. This article focuses on the appropriate use of methadone and buprenorphine, based both on the collective published literature and the clinical and research experiences of the authors, in the management of opioid-dependent pregnant women. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project began in 2005 to examine the comparative safety and efficacy of methadone and buprenorphine in the treatment of opioid dependence among pregnant women and their neonates. The MOTHER project is a double-blind, double-dummy, flexible-dosing, parallel-group clinical trial that involves eight clinical sites. It is the first large-scale study to formally examine the relative merits of each of the currently available opioid agonist agents in opioid-dependent pregnant women. Fig. 1 indicates that numerous issues need consideration when prescribing opioid agonist therapy and managing the opioid-dependent pregnant patient. This article is focused on the clinical issues relevant to management of opioid-dependent pregnant women prior to and during delivery. Thus, neonatal management including neonatal withdrawal is beyond the scope of this article.

## 2. Assessing the opioid-dependent pregnant woman

Patient assessment at treatment entry serves two purposes: (a) to establish rapport and trust with the individual and (b) to gather information to optimize treatment.

### 2.1. Assessment to build a therapeutic alliance

A pregnant woman expressing interest in receiving substance dependence treatment has taken a courageous step and should be treated accordingly. From first contact, every effort is needed to facilitate treatment entry. Timely assistance, scheduling flexibility, and appropriate empathy and optimism for change are needed. The common treatment resistance and demanding behaviors are best viewed as treatment challenges and normal parts of substance dependence. Blaming the mother for her previous behavior will not facilitate positive behavior change. Intake appointments should be completed within the same day or no later than 2 working days after first contact to significantly reduce the attrition rate between initial contact and the intake appointment (Festinger, Lamb, Kirby, & Marlowe, 1996; Festinger, Lamb, Kountz, Kirby, & Marlowe, 1995; Festinger, Lamb, Marlowe, & Kirby, 2002; Stark, Campbell, & Brinkerhoff, 1990; Stasiewicz & Stalker, 1999).

### 2.2. Opioid agonist medication history

Obtaining a medication and addiction treatment history will facilitate the selection of the optimal treatment strategy. Some patients who are already maintained on methadone or buprenorphine prior to conception may choose to remain on their current regimen, switch to the other medication, or seek medically assisted withdrawal (also known as detoxification or taper). Other patients will present naive to opioid agonist treatment. Factors to consider in choosing the best pharmacologic approach to treat these patients are discussed below (see Section 3). Declining medication-assisted treatment often results from the patient misunderstanding the effects of methadone or buprenorphine during pregnancy. Equally, misinformation may result from a health care provider who is unfamiliar with opioid dependence or from family or significant others who encourage the pregnant woman to avoid medication in an attempt to prevent medication-related harm to the fetus or neonatal abstinence syndrome (NAS) after delivery. Reviewing with the patient (and as appropriate, other concerned parties) the risks and benefits of opioid maintenance during pregnancy and the risks associated with medically assisted withdrawal for the mother and neonate allows a fully informed decision by the patient about the treatment.

### 2.3. Motivation for treatment

There are numerous reasons why patients seek or continue in opioid agonist treatment subsequent to pregnancy awareness. Clearly, the responsibility of raising a child and the changes in physiology associated with pregnancy can be powerful motivating factors for healthy behavior. Factors leading patients to treatment have been widely categorized into internal (e.g., mental anguish and sense of failure in professional and/or personal life) and external reasons (e.g., legal involvement). Motivating factors in opioid-dependent pregnant patients (Jones, O'Grady, Schlundt, & Tuten, Submitted a) paralleled the findings from a more general substance-abusing population, showing that severity of the substance problem itself and associated health problems were the strongest predictors of treatment readiness and entry (Handelsman, Stein, & Grella, 2005).

### 2.4. Assessment tools

Guidelines for comprehensive assessment of opioid-dependent pregnant and nonpregnant patients are available (Center for Substance Abuse Treatment [CSAT], 1993, 2005). These assessments focus on obstetric/gynecological status, nutrition, social functioning, and medical and

Table 1
Selected medications known to alter the effect of methadone or buprenorphine

| Indication and medication | Methadone effect | Buprenorphine effect | Reference |
|---|---|---|---|
| Alcohol abuse | | | |
| Disulfiram | No change in effect | No change in effect | George et al. (2000), Tong et al. (1980) |
| Naltrexone | Risk of opioid withdrawal | Risk of opioid withdrawal | Eissenberg et al. (1996), Kosten et al. (1990) |
| Anticonvulsant | | | |
| Carbamazepine | Decreased effect of methadone | No change in effect | Eap et al. (2002), Paetzold et al. (2000), Schlatter et al. (1999) |
| Antidepressants | | | |
| Desipramine | Increased serum levels of desipramine | No change in effect | Kosten et al. (1992), Oliveto et al. (1995) |
| Fluoxetine | Increased effect due to inhibition of opioid metabolism | No change in effect | Iribarne et al. (1998), Oliveto et al. (1995) |
| | The effect appears less prominent than that between fluvoxamine and methadone and may be unlikely to have clinical consequences | | Bertschy et al. (1996) |
| Fluvoxamine | Increased effect due to inhibition of opioid metabolism | Increased effect due to decreasing opioid metabolism | Bertschy and Baumann (1995), DeMaria and Serota (1999), Iribarne et al. (1998) |
| Antifungal agent | | | |
| Ketoconazole | Increased effect due to decreasing opioid metabolism; sedation is a problem | Increased effect due to decreasing opioid metabolism | Ibrahim et al. (2000), Kosten et al. (2002) |
| Anxiolytic | | | |
| Benzodiazepines (e.g., flunitrazepam) | Increased opioid effect | Increased opioid effect | Ernst et al. (2002), Kintz (2002a, 2002b), Kilicarslan and Sellers (2000), Reynaud et al. (1998), Singh et al. (1992) |
| Gastrointestinal | | | |
| Omeprazole | Increased effect of methadone reduced respiration in the rat | No change in effect | Kilicarslan and Sellers (2000) |
| Selected HIV protease inhibitors | | | |
| Atazanavir or atazanavir/ritonavir | No change in effect of methadone; no effect of methadone on AZT | Increased buprenorphine and buprenorphine metabolite concentrations and might require a decreased buprenorphine dose | Friedland et al. (2005), McCance-Katz et al. (2007) |
| Indinavir | Increased effect due to decreasing opioid metabolism | Increased effect due to decreasing opioid metabolism | Fornataro (1999), Iribarne et al. (1998) |
| Ritonavir | Alone has no clinical effect on methadone; combination lopinavir–ritonavir, showed methadone withdrawal and need for dose adjustment/effects on methadone metabolism varied | Increased effect due to decreasing opioid metabolism; increasing buprenorphine levels may not be clinically meaningful | Iribarne et al. (1998), McCance-Katz et al. (2003), Stevens et al. (2003) |
| Saquinavir | Increased effect due to decreasing opioid metabolism | Increased effect due to decreasing opioid metabolism | Iribarne et al. (1998b) |
| Nonnucleoside reverse transcriptase inhibitor | | | |
| Efavirenz | Decreased methadone effect, dose increase needed | Decreased buprenorphine levels but not enough to result in withdrawal | McCance-Katz et al. (2002, 2006) |
| Zidovudine (AZT) | Increased AZT effect (toxicity is possible but rare); no effect on methadone | No clinically meaningful change in AZT; no change in effect in buprenorphine | Iribarne et al. (1998), McCance-Katz et al. (1998, 2001) |
| Pain | | | |
| Partial opioid agonists | Risk of opioid withdrawal | Theoretical risk of withdrawal depending on type of partial agonist medication | Strain et al. (1993) |
| Parkinson's treatment | | | |
| Amantidine | No change in effect | No change in effect | Kosten et al. (1992), Oliveto et al. (1995) |

*Note*. This table provides examples of buprenorphine or methadone drug interactions and some selected references for these. The table is not intended to provide a comprehensive list of drug interactions with either medication. Please see CSAT *TIP #43* (2005) for more information.

psychiatric history. A comprehensive evaluation may start with the Addiction Severity Index (ASI; McLellan et al., 1992), an assessment instrument that examines seven domains of functioning affected by substance addiction, namely medical, legal, employment, alcohol, drugs, psychological, and family or social. Thus, the ASI is an assessment

tool that can inform treatment planning. Ideally, clinicians should use a version of the ASI tailored to women and pregnancy (Comfort, Zanis, Whiteley, Kelly-Tyler, & Kaltenbach, 1999). In addition to assisting with initial treatment planning, results of regular ASI assessments can aid in assessing treatment progress and addressing relapse, if it occurs. The ASI has predictive validity in pregnant patients, with greater medical and drug ASI problem severity being associated with longer treatment retention in intensive comprehensive care (Jones et al., Submitted a; Kissin, Svikis, Moylan, Haug, & Stitzer, 2004).

### *2.5. Objectives for treatment and stabilization of opioid agonist medication*

The objectives of the opioid agonist treatment for pregnant patients are similar to those for their nonpregnant counterparts: (a) to prevent opioid withdrawal signs or symptoms, (b) to provide a comfortable induction onto the medication, and (c) to block the euphoric effects of illicit opioids while also attenuating the motivation (i.e., craving, social interactions) to use illicit opioids and other drugs. In addition, there are pregnancy-specific objectives of eliminating fetal exposure to illicit opioids and other drugs and attempting to stabilize the intrauterine environment. Meeting these patient objectives may enhance treatment retention, particularly involvement in prenatal care, which is significantly associated with positive pregnancy and neonatal outcomes (Jones, 2006). By eliminating the illicit opioid and other drug use, the opioid-dependent patients can begin to focus on repairing relationships, obtaining fulfilling employment, and engaging in rewarding recreational activities. Moreover, the process of prenatal bonding with her unborn child takes on added significance. No medication has been found to change all the behaviors and psychiatric disorders associated with illicit drug use. Thus, behavioral and psychosocial interventions specific to the problems facing opioid-dependent pregnant women are vital for initiating and sustaining substance abstinence (Finnegan, 1991).

## 3. Initiation of opioid agonist medication in dependent pregnant patients

For opioid-dependent patients entering treatment upon pregnancy awareness, methadone is the “standard of care” (CSAT, 2005). Patients stabilized on methadone before pregnancy should remain on it, especially because there have been case studies associating such morbidities as stillbirth, fetal distress, and premature delivery with detoxification from methadone (Blinick, Wallach, & Jerez, 1969; Rementeria & Nunag, 1973; Zuspan, Gumpel, Mejia-Zelaya, Madden, & Davis, 1975). Furthermore, transition from methadone to buprenorphine introduces the possibility for destabilization, and the potential maternal and fetal risks of transferring a stabilized methadone patient onto buprenorphine have not been fully evaluated nor has a medication transition procedure that avoids withdrawal risk been developed.

Because methadone is the only medication recommended for opioid-dependent pregnant patients, buprenorphine should be prescribed only when the benefits outweigh the risks and the patient has refused methadone (CSAT, 2004). Thus, it is likely that many patients may be transferred from buprenorphine to methadone. On the basis of clinical recommendations for pregnant patients (Dunlop et al., 2003), the following approach is suggested. For patients maintained on 2 to 4 mg of buprenorphine, transfer to 20 mg methadone; for those maintained on 6 to 8 mg of buprenorphine, transfer to 30 mg methadone; and for those maintained on 8 mg or more of buprenorphine, an initial dose of 40 mg methadone is suggested. Higher initial methadone doses are not recommended on the first day due to concerns regarding oversedation. This first dose should be followed with observations, and clinical judgment should be used for initial and subsequent doses. Because of the residual blockade from buprenorphine, it is possible that the subsequent doses could be less than the total Day 1 dose.

Although buprenorphine has not been approved by the FDA for use in pregnancy, the reality is that the introduction of buprenorphine has provided an additional treatment option for nonpregnant patients and increased the opportunity for patients to potentially become pregnant while using this medication (CSAT, 2005). One aim of the MOTHER trial is to gain experience with buprenorphine during pregnancy and compare maternal and neonatal outcomes to a similar methadone group. These results may provide adequate data for the FDA to review the suitability of using these medications during pregnancy.

If the clinician determines that the risk–benefit ratio favors buprenorphine, Subutex (buprenorphine alone) is the preferred medication over Suboxone (buprenorphine + naloxone). Subutex is preferred for two reasons. The first is to avoid prenatal exposure to naloxone. Preclinical data suggest that fetal naloxone exposure produces maternal and subsequently fetal hormonal changes (Brunton et al., 2005; Douglas, Meddle, Toschi, Bosch, & Neumann, 2005). The second is to reduce the likelihood of precipitating maternal and fetal withdrawal if buprenorphine was crushed and injected. For stabilized Suboxone patients, guidelines recommend transfer to Subutex following confirmation of pregnancy (CSAT, 2005). However, data to support the safety and efficacy of this recommendation are not currently available. Furthermore, the risk of diversion of take-home Subutex needs consideration.

When prescribing either methadone or buprenorphine, it is important to review with patients the need to avoid both licit and illicit drugs for their health, treatment success, and potential interaction of the medication with these substances (e.g., these drugs in combination with alcohol or benzodiazepines can be fatal; White & Irvine, 1999). Table 1 shows that the potential for drug interactions exists. Thus, as with

all pregnant patients, consideration needs to be given when additional medications are prescribed, especially in regard to their potential incompatibility with opioid agonist therapy.

## 4. Induction

Guidelines for inducing pregnant patients to methadone have been well established in several publications (CSAT, 1993, 2005; Kaltenbach et al., 1998). One must ensure that the patient is not concurrently using other drugs that could increase the risk of oversedation. Care should also be taken to avoid increasing the dose too quickly or slowly to minimize overdosing and to forestall potential premature termination from treatment due to the inability of the medication to alleviate withdrawal, respectively. The quality of the therapeutic alliance with the health care providers initially established during assessment can help with retention.

The initial daily dose of methadone should be 10 to 30 mg. The lower dose may be suitable for women who are primarily dependent on short-acting oral opioids such as codeine, hydrocodone, and oxycodone. If the patient should experience withdrawal within a few hours, additional doses of 5 to 10 mg every 4 to 6 hours while the patient is awake may be administered for breakthrough withdrawal. It is vital not to misinterpret nonspecific distress associated with life situation or pregnancy as withdrawal or withhold needed methadone if bone fide withdrawal is present. It takes 4 to 5 days to reach steady state for methadone. Thus, caution must be used to base dose increases on symptoms at peak methadone levels (i.e., 2–4 hours after administration) rather than how long the effects last; otherwise, as methadone accumulates over the first 3 to 7 days, overdose may occur (Srivastava & Kahan, 2006). Therefore, total daily doses should not be increased any more frequently than every 3 to 5 days. The dose should be titrated up to the optimal dose where the patient experiences no withdrawal for at least 24 hours after a dose, uses no other opioid, and experiences minimal or no cravings. A standardized assessment of withdrawal such as the Clinical Opiate Withdrawal Scale (Wesson & Ling, 2003) or Clinical Institute Narcotic Assessment Scale for Withdrawal Symptoms (Peachey & Lei, 1988) is helpful to quantify withdrawal. However, some withdrawal symptoms (e.g., nausea, backache, etc.) overlap with pregnancy symptoms, and no instruments are currently available to disentangle the two medical conditions. This is where clinical judgment supersedes assessment tools. Often, a patient who has experienced opioid withdrawal previously when not pregnant can guide the prescribing care provider with whom an effective therapeutic alliance has been established.

For buprenorphine, the more complex pharmacology (mu partial agonist / kappa antagonist) may make induction more challenging, especially if the patient is actively using it at the time of first assessment. If the first dose of buprenorphine is administered too soon after the last opioid intake (prior to manifestation of clinical symptoms of opioid withdrawal, which can be numerous hours if long-acting opioids were used) or in too high a dose, there is a potential for significant precipitated withdrawal. As with methadone, if the buprenorphine dose is too low, it may not relieve withdrawal symptoms completely or for 24 hours until the next dose is due (e.g., Lintzeris, Ritter, Dunlop, & Muhleisen, 2002). Unlike methadone, buprenorphine has the added complexity of possibly precipitating withdrawal.

In opioid-dependent pregnant patients in the second trimester, transition from slow-release morphine or methadone to buprenorphine resulted in a "transient dysphoric mood status" that was observed for 2 days, similar to reports in nonpregnant patients (Eder et al., 1998). Similar to nonpregnant patients, allowing at least 6 hours between short-acting opioids and buprenorphine administration (i.e., a time when some objective signs of opioid withdrawal are present) was found to improve the tolerability of induction onto buprenorphine (Johnson, Jasinski, & Milio, 2005).

Identifying the optimal timing of the initial buprenorphine dose for patients taking long-acting opioids (e.g., MS Contin, OxyContin, and methadone) is more difficult. The few reports of transferring opioid-dependent pregnant women from methadone directly to buprenorphine (which we are not recommending at this time) indicated that it is possible (but not advised) to transition pregnant women in the second or third trimester from oral methadone (up to 85 mg) doses to sublingual buprenorphine (up to 12 mg). The major complaint due to this transition was dysphoric mood (Fischer et al., 1998, 2000) and "clearheaded" status (Jones, Suess, Jasinski, & Johnson, 2006).

Our own experience with pregnant women has shown that rapid induction onto 12 to 14 mg of buprenorphine in 2 to 3 days can be accomplished in pregnant women (e.g., Fischer et al., 2006; Jones et al., 2005). Ideally, doses should be based upon the severity of opioid dependence. The safety of buprenorphine makes it less likely to result in sedation.

Regardless of whether patients are inducted onto methadone or buprenorphine, ancillary medications that are safe for use during pregnancy and may ease the common symptoms of withdrawal are listed. Acetaminophen (Tylenol) is given for aches and pains. Antacids (Tums) are given for indigestion. Loperamide (Imodium A-D) may be given for diarrhea. Docusate sodium (Colace) may be given for constipation. Hydroxyzine (Vistaril) may be given for anxiety or restlessness. Diphenhydramine hydrochloride (Benadryl) may also be given for anxiety and restlessness. Educating patients regarding behavioral methods to control some symptoms may minimize medication use.

## 5. Stabilization

The same dosing criteria can be used for both nonpregnant and pregnant patients. Methadone stabilization protocols and recommended dose adjustment guidelines are available in the

CSAT *TIP #43* (CSAT, 2005). Based on its long half-life, methadone is generally administered once daily. However, methadone-maintained pregnant women frequently complain of increasing withdrawal symptoms as pregnancy progresses and thus may need elevations of their dose to maintain therapeutic plasma levels and prevent relapse and breakthrough withdrawal signs and symptoms. Kreek, Schecter, and Gutjahr (1974), Kreek (1979), and Kreek (1986) and others (e.g., Gazaway, Bigelow, & Brooner, 1993) have demonstrated that, for a given dose of methadone, plasma levels are significantly lower and withdrawal symptoms are increased during the third trimester compared with earlier trimesters. The reduced plasma levels coincide with increased methadone metabolism and faster clearance of methadone during the third trimester (Pond et al., 1985). A serum trough level of 0.24 mg/L or greater of methadone should be adequate to prevent withdrawal symptoms in pregnancy (Drozdick, Berghella, Hill, & Kaltenbach, 2002). Ideally, blood methadone levels should be coupled with clinical response to determine dose changes.

If single daily doses fail to mitigate withdrawal, split dosing is an option. The total daily dose is given in two divided doses separated by at least 8 hours. Split dosing may be advantageous in the third trimester of pregnancy, when metabolism of methadone and clearance rates increase and steady-state methadone levels decline; DePetrillo and Rice (1995) found less third trimester illicit opioid and cocaine use in split- versus single-dosing groups (0.5% and 0.3% vs. 24% and 15%, respectively). The benefits of split dosing may include less inhibition of fetal movement and breathing than is observed following a single daily methadone dose (Wittmann & Segal, 1991). Given buprenorphine's long biological half-life and unique pharmacology, it is anticipated that split dosing will not be necessary.

For buprenorphine stabilization, doses between 4 and 24 mg per day may be appropriate for nonpregnant patients (Chiang & Hawks, 2003); however, there is no recommended minimum or maximum dose in the buprenorphine product insert. This circumstance is due in part to variability in sublingual absorption of buprenorphine (Chiang & Hawks, 2003), its subsequent metabolism, and patient response. As with methadone, the primary goal in choosing a stable dose of buprenorphine for a given patient should be to attain a level that suppresses opioid withdrawal effects and, hence, provide the best opportunity to retain the patient in treatment.

In randomized double-blind studies, dose increases during the course of pregnancy for both methadone and buprenorphine were an average of three-unit increases (totaling averages of 30 mg for methadone and 6 mg for buprenorphine; Jones et al., 2005). Although there has been considerable research investigating the parameters of buprenorphine dosing in nonpregnant patients (e.g., Amass, Bickel, Crean, Blake, & Higgins, 1998; Amass, Bickel, Higgins, & Badger, 1994; Amass, Kamien, & Mikulich, 2000, 2001; Bickel, Amass, Crean, & Badger, 1999; Greenwald, Schuh, Hopper, Schuster, & Johanson, 2002; Petry, Bickel, & Badger, 2000, 2001), similar research has not yet been conducted in pregnant patients. Given the extended biological half-life buprenorphine by virtue of slow dissociation from the mu receptor, blood volume changes with pregnancy might be less problematic than with methadone maintenance.

## 6. Preventing and managing relapse

The best approach to relapse is to recognize the patient's warning signs before drug use occurs and monitor urine drug screens regularly. The patient's clinical presentation at each visit should be noted for changes that suggest precursors to relapse. Careful probing will often reveal a pattern of the patient's drug use (e.g., related to specific recurrent stressors). Strategies to help the patient modify her patterned responses to stressors can be implemented. The use of a functional analysis with patients is especially beneficial for determining the where, when, why, and who of drug use (see Meyers & Smith, 1995 for guidelines for implementing this assessment method). Careful observation and review of patient behavior (e.g., changes in clinic attendance) can help prevent a lapse before it starts. If drug use is admitted or detected, acknowledge it in a nonjudgmental way, neither punishing nor condoning the behavior. Acknowledge the lapse and praise the patient for preventing it from becoming a relapse. Reviewing the functional analysis and then implementing treatment plan changes may prevent continued drug use by the patient. Although any drug use is a matter of concern, which drug a patient uses is also a key to determine areas for treatment plan revision. If a patient is using additional opioids, a dose increase may be needed. If she does not appear in withdrawal and reports her dose is adequate, yet continues to use opioids, it is important to determine what factors contribute to the maintaining of such a behavior (e.g., using opioids because her significant other does not want to use opioids alone). If nonopioids are being used, the dose of her medication may not require an adjustment because methadone and buprenorphine only treat opioid dependence; however, the role that opioid abstinence symptoms are playing in this behavior (e.g., benzodiazepines or alcohol used to self-medicate anxiety or other withdrawal symptoms) needs consideration. There is a risk for overdose when high doses of benzodiazepines are combined with opioids. In the case of alcohol dependence, inpatient medically assisted withdrawal using benzodiazepines with frequent fetal monitoring may be needed. In the case of benzodiazepine dependence, these drugs should be tapered only very slowly if possible. Care should be taken to avoid precipitating hypnosedative withdrawal because this is very detrimental to both mother and fetus (Einarson, Selby, & Koren, 2001). Antabuse, because of its teratogenic effects, and naltrexone, because of its ability to precipitate severe opioid withdrawal in patients taking methadone or buprenorphine, must be avoided during pregnancy. The concomitant abuse of nonopioid licit and illicit drugs is an issue that should be address clinically. Although

agonist medication dose reductions may be required for patient safety in the case of chronic benzodiazepine abuse, decreasing a patient's dose as a "punishment" for other drug use is not appropriate medical care and creates vulnerability for relapse to use of opioids. Promising behavioral treatments to address concomitant licit and illicit substance abuse include cognitive–behavioral therapy (Carroll et al., 2006, Rawson et al., 2002) and contingency management (e.g., Lussier, Heil, Mongeon, Badger, & Higgins, 2006), with the combination producing the most optimal outcomes (Carroll et al., 2006, Rawson et al., 2002).

## 7. Ensuring comprehensive care

Methadone maintenance combined with prenatal care and a comprehensive drug treatment program can improve many of the detrimental maternal and neonatal outcomes associated with untreated heroin abuse (Connaughton, Resser, Schut, & Finnegan, 1977; Kandall et al., 1977). Although ethical concerns do not allow a random assignment to a no-treatment or an inadequate-treatment control group, the available literature suggests that buprenorphine given in a comprehensive care setting would be associated with benefits similar to those observed with methadone. Necessary elements that comprise comprehensive care for this patient population have been reviewed (e.g., Finnegan, 1991; Kaltenbach et al., 1998). Because most research on opioid dependence during pregnancy includes low socioeconomic patient samples needing multiple medical and psychosocial services, it is possible that those pregnant women entering office-based buprenorphine treatment may require different components in comprehensive care to optimize their treatment response.

## 8. Agonist medication management during labor and delivery

Clinical experience and limited case reports suggest that to avoid withdrawal, agonist medications should be continued without interruption (e.g., daily dosing) during labor and delivery and the immediate postpartum period (CSAT, 2005; Jones, Johnson, & Milio, 2006). If there is a need to keep the patient "nil per os" due to the likelihood of an operative delivery requiring anesthesia, the methadone can be administered in a very small volume of juice (i.e., 20–30 ml). If there is concern that the methadone dose may slow down the labor, observed split dosing is an option. The remaining dose should be administered at the first symptoms of withdrawal. Buprenorphine is associated with minimal spontaneous withdrawal; thus, withholding a dose is possible if needed. Providing buprenorphine intramuscularly in a dose equivalent to that given sublingually is another alternative.

## 9. Pain medication management during labor and delivery and recent postpartum

Buprenorphine dosing during labor and delivery is complicated by its pharmacologic profile. The human mu opioid receptor occupancy is dose related: 27% to 47% at 2 mg/day and up to 89% to 98% at 32 mg/day (Greenwald et al., 2007). The slow dissociation and low intrinsic activity of buprenorphine at the mu receptor (Cowan, 1995) result in an enhanced safety profile. These same pharmacologic characteristics potentially complicate adequate maternal delivery and postpartum pain relief because pain medications may not be able to adequately reach the target receptors. The approach to treating pain in buprenorphine-maintained nonpregnant patients may include discontinuing buprenorphine and treating with full-scheduled opioid agonist analgesics by titrating to effect to avoid withdrawal and then to achieve analgesia (e.g., sustained-release and immediate-release morphine or other opioid agonist analgesics), or if the pain is not severe, dividing the total buprenorphine dose into small doses given every 6 to 8 hours to take advantage of its analgesic properties. When using opioids, higher doses than typical doses may be required to displace buprenorphine from the mu opioid receptor (Alford, Compton, & Samet, 2006).

The maintenance medication provided to treat opioid dependence is usually inadequate for pain management. Regional analgesia (e.g., epidural) can provide adequate pain relief in women receiving methadone or buprenorphine who choose to have analgesia for childbirth or require analgesia for cesarean delivery. Commonly used opiate agonist or antagonist medications such as nalbuphine (Nubain) or butorphanol (Stadol) are contraindicated, as opiate withdrawal may be precipitated in the opiate-dependent patient. Nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen rather than opioids are recommended for postpartum management of moderate pain in buprenorphine-treated patients (Dunlop et al., 2003). Opioids in combination with acetaminophen and a NSAID are suggested for methadone-maintained patients (Dunlop et al., 2003). Women maintained on methadone required approximately 70% more opiate analgesic following cesarean delivery as compared with nonopiate-dependent control patients, particularly in the first 24 hours following delivery. Opiate utilization was similar following vaginal birth, despite higher pain scores in the methadone-maintained patients (Meyer, Wagner, Benvenuto, Howard, & Plante, 2007). Women maintained on buprenorphine required less opiate analgesia following vaginal birth, with a nonsignificant increase in opiate utilization and pain scores following cesarean delivery (Meyer, Paranya, Kristensen, & Plante, 2007). The lack of increased opioid utilization may be due to a ceiling effect and suggests the need for prospective studies in this area. Case reports of buprenorphine- or methadone-treated patients who delivered via C-section suggested that

routine opioid analgesic doses delivered via a patient-controlled analgesia pump 24 hours after surgery are effective in reducing postpartum pain (Jones et al., 2006). Because most opioid-dependent patients require greater-than-typical doses of opioid analgesics for pain management (Gunderson & Stimmel, 2004), individualized pain control is needed. Ideally, patients and anesthesiologist should discuss pain management options well before delivery. Clear explanations and reassurance that their pain will be adequately managed likely reduce distress and opioid requirements.

## 10. Postdelivery phase

### *10.1. Agonist medication management*

Following delivery, consensus statements recommend maintaining patients on methadone doses similar to levels received prior to pregnancy, but patients frequently wish to be medication-free upon delivery of the child. Patients should be advised of the stresses of early motherhood, the likelihood of relapse during medication tapering, and the desirability of continuing agonist treatment. Postpartum methadone doses are recommended to be reduced to half the dosage required in the third trimester (CSAT, 2005). These recommendations may depend on the amount of methadone received during pregnancy. One report of 10 patients found that of those women maintained on doses between 25 and 100 mg, only one showed mild signs of overmedication within 3 days after delivery (Jones, Johnson, O'Grady, Jasinski, & Milio, in press). Given the large individual variability among patients, dose changes should be guided by signs and symptoms of over- or undermedication (Kaltenbach et al., 1998).

### *10.2. Evaluation and treatment of NAS*

Neonates exposed to opioid agonists in utero are prone to display a NAS often requiring medical management. However, a discussion of the assessment and management of NAS is outside the scope of this article.

### *10.3. Breast-feeding*

Breast milk is the most complete form of nutrition for infants, with a range of benefits for health, growth, immunity, development (U.S. Department of Health and Human Services, 2000a, 2000b; Virden, 1988; Widstrom et al., 1990), and societal cost savings (Cohen, Mrtek, & Mrtek, 1995). Although the overall amount of methadone in breast milk appears to be low, ranging from 21 to 314 ng/ml, and not related to maternal methadone dose (Jansson, Dipietro, Elko, & Velez, 2007), ingesting breast milk relative to formula has been found to be associated with less severe NAS (Abdel-Latif et al., 2006). Thus, breast-feeding is compatible with methadone and should be encouraged. Gradual weaning from the breast is recommended because at least two infants appeared to develop NAS following abrupt discontinuation of breast-feeding by women receiving 70 and 130 mg of methadone, respectively (Malpas & Darlow, 1999). Incompatible conditions with breast-feeding include an HIV-positive status and/or continued ingestion of illicit drugs and/or alcohol. Hepatitis C is not a contraindication for breast-feeding. Patients who smoke cigarettes should be counseled as to the morbidities associated with neonatal nicotine exposure as well as the negative effects of smoking on health.

Buprenorphine is excreted in breast milk, and levels are similar or higher than levels observed in the blood; the apparent plasma-to-milk ratio is approximately 1 (Johnson et al., 2001). This ratio gives guidance to providers in estimating the total daily buprenorphine consumption of the infant. Given the low oral bioavailability of buprenorphine, infant exposure will be only one fifth to one tenth of the total amount of buprenorphine available (Johnson, Jones & Fisher, 2003). Thus, buprenorphine levels in breast milk may have little effects on NAS (Auriacombe & Loustauneau, 2000).

## 11. Other clinical issues

### *11.1. Methadone and buprenorphine interactions with other medications*

To the best of our knowledge, there have been no prospective drug interaction studies conducted in pregnant women maintained on either methadone or buprenorphine. In the absence of such data, it is logical to consider that the known drug interactions summarized in Table 1 may also occur in pregnant women. However, there are maternal physiological changes (e.g., gastroinstetinal motility slowing, tidal volume, and pulmonary blood flow increases) as well as placental (e.g., metabolism and blood flow) and fetal (e.g., liver enzyme and albumin development) factors that could alter drug metabolism and drug interactions (Wunsch, Stanard, & Schnoll, 2003). Because drug interactions may occur at the site of aromatase formation and activity (Nanovskaya et al., 2004; Zharikova, Deshmukh, Nanovskaya, Hankins, & Ahmed, 2006), an investigation of placenta exposure to methadone or buprenorphine did not appear to inhibit estrogen formation at a level that is likely to alter maternal or neonatal outcomes (Zharikova et al., 2007).

Because methadone has been a part of the treatment for opioid dependence for several decades, substantial information that documents its interaction with other medications exists. Depending on the medication, the dosing of either methadone or the concomitant medication will need to be adjusted.

In general, buprenorphine appears to have fewer significant drug interactions than methadone because it has low affinity for the 3A4 isoenzyme, which is responsible for

the metabolism of many drugs by the Cytochrome P-450 system (Iribarne et al., 1998; Iribarne, Picart, Dréano, & Bail, 1997; Iribarne, Picart, Dreano, & Berthou, 1998). When drug interactions do occur, they appear to increase the effects of buprenorphine (i.e., decreasing buprenorphine metabolism) and can be mitigated by a buprenorphine dose reduction. Similar to methadone (Ernst et al., 2002), concurrent intravenous or very high dose use of buprenorphine and benzodiazepines is associated with overdose deaths (e.g., Kintz, 2002a, 2002b; Reynaud, Petit, Potard, & Courty, 1998; Singh, Mattoo, Malhotra, & Varma, 1992). The interaction mechanism does not appear to be pharmacokinetic (Kilicarslan & Sellers, 2000). Finally, it should be noted that the interaction of sublingual buprenorphine and oral benzodiazepines is unclear.

Pharmacodynamic and pharmacokinetic interactions of buprenorphine with other medications are generally predicted and observed to be similar to those of methadone with other medications (e.g., increased sedation), although of lesser magnitude because buprenorphine as a partial agonist has lower maximal activity at the mu receptor (see Table 1).

### *11.2. Managing co-occurring psychiatric disorders*

There is a high prevalence (56%–73%) of co-occurring Axis I disorders in drug-dependent pregnant women (Burns, Melamed, Burns, Chasnoff, & Hatcher, 1985; Fitzsimons, Tuten, Vaidya, & Jones, 2007; Haller et al., 1993; Regan, Leifer, Matteucci, & Finnegan, 1982). Mood disorders during pregnancy have been associated with adverse maternal health behaviors, a high risk of postpartum depression, and behavioral effects on the offspring (Bonari et al., 2004; Cohen, Nonacs, Viguera, & Reminick, 2004). Thus, opioid-dependent pregnant patients should be screened for and given appropriate medication and behavioral treatments for their disorders.

Pharmacotherapy use should be based on a positive risk–benefit ratio and not include drugs known to have teratogenic effects such as dilantin (Meador et al., 2006). Selective serotonin reuptake inhibitors (SSRIs) should be used as necessary but with caution that there might be a risk of pulmonary hypertension, an uncommon disorder in the neonate, or frank SSRI toxicity that is rarely fatal (Chambers et al., 2006; Kulin, Pastuszak, & Koren, 1998). Fluvoxamine induces methadone metabolism, and if not avoided, methadone doses should be modified. Benzodiazepines should not be administered due to their high risk of dependence in this population.

For patients with a history of sexual abuse, flashbacks, intense emotions, and negative memories may occur during key treatment times including medication induction and labor and delivery. Appropriately trained staff can help the patient identify and cope with these traumatic memories and increase her opportunities to remain in treatment and be drug free (Records & Rice, 2005). Finally, the need for psychotropic medications may be lessened by appropriate use of opioid agonists because they may have significant antidepressant or anxiolytic effects.

## 12. Summary

In summary, our understanding and knowledge about the treatment of opioid dependence during pregnancy have grown in the last 40 years. In that time, data have supported the need for adequate methadone-dosing regimens. The understanding of the complexities of this disorder and that of polydrug addiction during pregnancy has grown, and informed treatment strategies have been established. No longer are pregnant women excluded from agonist maintenance treatment, rather, they often receive first priority because the benefits considerably outweigh the risks. The substance dependence treatment field is now converging to view the risks and benefits of treatment of opioid dependence with both the mother and child as equally important rather than competing against each other. Moreover, the advent of buprenorphine has brought both a new treatment option and unique challenges to treatment, not only in terms of dose induction and pain management but also the need for rational decisions about whether methadone or buprenorphine may be most appropriate for a given clinical situation. Finally, the MOTHER study represents a major advance toward using evidence-based data to drive optimal treatment approaches tailored to the needs of each opioid-dependent pregnant patient.

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