



Pharmacotherapy for pregnant women with addictions

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Objective: Dependence on alcohol, nicotine, or illicit drugs during pregnancy continues to be a problem of major medical, social, and fetal consequences. The purpose of this systematic review was to summarize current experience that pertains to pharmacotherapy for pregnant women with specific chemical addictions.

Study design: Studies were identified through Medline and HealthSTAR (1979-2003) that linked specific pharmacotherapy with pregnancy. This article reviews the English language literature for clinical studies that link the 2 conditions. In addition, reference lists of all articles that were obtained were evaluated for other potential citations.

Results: Pregnant women are excluded systematically from almost all drug trials. Most knowledge about the fetal effects from maternal substance and medication use comes from animal data and from case reports and small clinical series. With the exception of methadone and nicotine replacement, clinical experience with antiaddictive medications in pregnant women is either very limited (alcohol, stimulants) or nonexistent (cannabis, hallucinogens).

Conclusion: Antiaddiction medications are important in the treatment of pregnant women with opioid and nicotine dependence and are of growing importance in the treatment of alcohol and stimulant dependence. Future directions will be toward increasing knowledge about current drug therapy and in developing new antiaddiction medications.

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Few studies have examined the efficacy of any antiaddictive drugs in women with substance use disorders. In 1994, the National Institute on Drug Abuse convened a conference to address the wide gender gap in scientific knowledge about addiction.¹ Obstacles to conducting addiction research in women include the pharmaceutical industry's hesitation to conduct trials

among reproductive aged women, particularly when they wish to become or are already pregnant.

A proportion of women with substance dependence or abuse will continue using addictive substances, despite an awareness of potential harm to the fetus. Psychosocial treatments (eg, counseling, psychotherapy, and mutual help) provide the core of most addiction treatment programs. In addition, pharmacotherapies for certain addictions are available, although others are in development.

This report summarizes the English language literature about pharmacotherapy for pregnant women with addictions. Our primary intent is to familiarize obstetric providers with recent developments in pharmacotherapy

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so that they can advise their patients optimally about alternative treatments and their limitations. We searched Medline and HealthStar databases for a 25-year period (1979-2003), combining keywords "pregnancy" with names of specific antiaddictive medications that are either existing or hold promise. Reference lists of all full-length English articles were evaluated for other potential citations.

Substance use during pregnancy

Substance use is most prevalent in reproductive-aged people. In a survey among women aged 15 to 44 years, almost 90% of the women drank alcohol; approximately 44% of the women smoked marijuana, and at least 14% of the women used cocaine.¹ Women have an estimated lifetime prevalence of 17.9% and a 12-month prevalence of 6.6% for any substance use disorder (excluding nicotine dependence). Although substance use disorders are still more prevalent in men than in women, comparable rates of alcohol, tobacco, cocaine, and heroin use are now being recorded among boys and girls aged 12 to 17 years.² This finding is particularly disturbing because women have a heightened vulnerability to the medical, physical, mental, and social consequences of substance use.³

Rigorous epidemiologic studies with diagnostic criteria for substance abuse and dependence have not been done in pregnant women, so the prevalence rates of addictions to specific substances during pregnancy are largely unknown. However, several surveys have quantified the frequency of substance use among pregnant women. Patient interviews and urine toxicologic testing at the initial prenatal visit and at delivery suggest that substance use during pregnancy ranges from 0.4% to 27%, depending on the population surveyed.⁴⁻⁶ This finding is not surprising, because more than one third of the total adult population who were interviewed admitted to some illicit drug use.⁷ Based on the combined 2000 and 2001 national household survey on drug abuse samples among pregnant women aged 15 to 44 years, 3.7% of the women reported using illicit drugs in the month before their interview.² This rate was significantly lower than the rate among women aged 15 to 44 years who were not pregnant (8.3%). In pregnant women aged 15 to 17 years, however, the rate was 15.1%, which is slightly greater than the rate for nonpregnant women of the same age (14.1%).²

The National Pregnancy and Health Survey, a National Institute of Drug Abuse—conducted nationwide survey, reported that 5.5% of the 4 million women who gave birth in the United States in 1992 used illegal drugs while they were pregnant.^{8,9} Marijuana and cocaine were used most frequently. The survey also reported a strong link between cigarette smoking and either

alcohol or illicit drug use. Despite a generally decreasing trend in substance use during gestation, women did not discontinue their dependence completely. This finding suggests that pregnancy may be an invaluable opportunity to screen, educate, and refer these patients for treatment.

Fetal effects from substance abuse

Unbound drugs and metabolites generally cross the placenta easily and enter into the fetal central nervous system. Our search revealed that most knowledge about the effects of these substances on embryonic/fetal development comes either from animal data or from case reports, adverse event reports, or small clinical series in humans. For most substances of abuse, data are either insufficient or inconsistent, which prevents the identification of a causal relation between a specific substance and a particular perinatal outcome.

Animal and human studies each present significant methodologic challenges. Doses that are used in animal experiments are typically >10 times the customary human dose. Furthermore, these animals when sedated may eat less or behave abnormally. Isolated reports in humans are confounded by the use of other multiple illicit substances, potentially unhealthy lifestyles of the mother, and a lack of a control group for comparison.

Accurate assessments of doses and exact periods of exposure to any substance are often not possible. In many cases, evidence is lacking to distinguish between environmental factors (eg, poverty and the corresponding poor nutrition, lack of access to prenatal care) and substance abuse—related effects in the fetus. Substances of abuse may be taken at toxic doses. The impurity of most street drugs and the common practice of using multiple substances make it particularly difficult to ascribe specific effects to a certain substance.

Table I lists such effects, with the findings from ≥ 2 reports in humans.¹⁰ Exposure to specific substances, especially if long term, place the fetus at risk for low birth weight, small head circumference, prematurity, and other developmental complications. The risk of structural anomalies, specifically or overall, is not believed to increase in most circumstances.

Principles of treatment during pregnancy

In treating pregnant women with a substance dependence, psychologic and pharmacologic treatments are often intertwined. Effective psychosocial treatments for women with addictions are many: contingency treatment, community reinforcement, behavioral marital therapy, cognitive behavioral skills training, motivational enhancement therapy, 12-step approaches, and "seeking safety" (a therapy designed for addicted women with co-occurring post-traumatic stress disorder).

Table I Impact of substances on the fetus and neonate, according to ≥ 2 reports in humans

Substance	Impact
Alcohol	Abortion, microcephaly, growth deficiency, central nervous system dysfunction including mental retardation and behavioral abnormalities, craniofacial abnormalities (ie, short palpebral fissures, hypoplastic philtrum, flattened maxilla), behavioral abnormalities
Cigarettes	No anomalies, intrauterine growth restriction (200 g lighter), preterm birth, placenta previa, placental abruption, reduced risk of preeclampsia
Cannabis: Marijuana, delta-9-tetrahydrocannabinol, hashish	No anomalies, reduction of 0.8 weeks in the length of gestation, corresponding decrease in birth weight, subtle behavioral alterations
Central nervous system stimulants: Antiobesity drugs, methamphetamines, cocaine, methylphenidate, phenmetrazine	Abortion (?), hyperactivity in utero, congenital anomalies (heart?, biliary atresia?), depression of interactive behavior, urinary tract defects, symmetric growth restriction, placental abruption, cerebral infarction, brain lesions, fetal death, neonatal necrotizing enterocolitis
Narcotics: Codeine, heroin, hydromorphone, meperidine, morphine, opium, pentazocine, tripeleminamine	Fetal growth restriction, no anomalies, intrauterine withdrawal with increased fetal activity, depressed breathing movements, preterm delivery, preterm rupture of the membranes, meconium-stained amniotic fluid, perinatal death

As with all medications taken during pregnancy, the decision to prescribe an antiaddictive medication must be guided after the benefits are weighed with potential risks, based on clinical acumen and limited outcomes information. To qualify for antiaddictive pharmacotherapy, patients must meet criteria for dependence on the substance in question. In addition, there must be no contraindication to the medication, and the patient must understand the risks and benefits of its use. In general, the dosing regimen of each drug would be the same for pregnant women as for others, with use of the lowest effective dose for each individual's needs.

Not all persons with an addictive disorder qualify for drug therapy. Currently, there are no Food and Drug Administration (FDA)-approved medications available for detoxification or maintenance therapy for patients who are dependent on stimulants, hallucinogens, cannabis, or inhalants (eg, glue, paint, hairspray).

Pharmacotherapy for addiction can be divided into 2 categories: (1) detoxification to reduce or to prevent withdrawal symptoms and (2) maintenance to avoid relapse or to reduce the amount of substance use if relapse occurs. Table II lists signs and symptoms of withdrawal for different groups of addicting substances. These signs may be subtle and mistaken easily for adaptive changes because of pregnancy. There is comorbidity between psychiatric disorders and substance use, particularly among women. Although pharmacotherapy for affective or anxiety disorders is useful for ameliorating psychiatric symptoms, research is mixed on its effectiveness for improving alcohol- and drug-related outcomes.¹¹ Women with co-occurring psychiatric and substance use problems are challenging to engage and retain in care. Particular attention should be focused on screening and assessment of alcohol and drug use and on problem severity among pregnant women who have identified

psychiatric disorders or who are receiving antidepressant or anxiolytic medications.

Table III lists currently available medications that are prescribed as antiaddictive therapy during pregnancy. Standard dosage regimes, common side effects, and clinical considerations are mentioned. We included only those medications in which clinical trials during pregnancy are reported.

Virtually all antiaddiction medications are thought to pass into breast milk.¹⁰ Although the concentration may be low, exposure to the breast-feeding infant with prolonged daily dosings would be unsafe. A commonly asked question about breast-feeding is "Which would be safer, the known exposure to an antiaddictive medication or the uncertainty of exposure to an abused substance?" In our experience, very few women with continued illicit drug use wish to breast-feed.

Alcohol dependence

Alcohol affects several neurotransmitter systems, including gamma-aminobutyric acid, glutamate, serotonin, dopamine, norepinephrine, and endogenous opioid systems. All receptors are believed to be present in the fetus from early in gestation. A stepwise treatment plan for detoxification followed by minimizing relapse is proposed.

Detoxification

Benzodiazepines remain a first-line therapy for alcohol withdrawal. All members of the benzodiazepine class act at their own receptors, which are coupled with the gamma-aminobutyric acid-A receptor. This receptor complex mediates an increase in inhibitory neurotransmission that counteracts the excitatory state of the brain in alcohol withdrawal. Longer-acting agents, such as

Table II Signs and symptoms of withdrawal from specific addictive substances during pregnancy

Additive substance	Signs/symptoms of withdrawal
Alcohol	Agitation, tremors, sleep disturbance, tachycardia, hypertension, nausea, dilated pupils, seizures
Cannabis, marijuana, delta-9-tetrahydrocannabinol, hashish	Restlessness, irritability, mild agitation, insomnia, nausea, cramping
Cigarettes	Irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings, drowsiness
Central nervous system sedatives-hypnotics: Alprazolam, barbiturates, chlordiazepoxide, diazepam, flurazepam, glutethimide, meprobamate, methaqualone, etc	Tremulousness, insomnia, chronic blink reflex, agitation, toxic psychosis, seizure, anxiety, agitation, muscle cramps, sleep disturbance, hypertension, fever, anorexia
Central nervous system stimulants: Methamphetamines, cocaine, methylphenidate, phenmetrazine, dimethyltryptamine, phencyclidine (PCP)	Muscle aches, abdominal pain, hunger, prolonged sleep, suicidal ideation, bradycardia, craving, depression
Opiates: Codeine/oxycodone, heroin, hydromorphone, meperidine, morphine, opium, pentazocine, tripeleennamine	Flu-like syndrome, agitation, dilated pupils, abdominal cramps, insomnia, anxiety, craving, tachycardia, hypertension

chlordiazepoxide, provide a smoother withdrawal during pregnancy, with fewer breakthroughs or rebound symptoms, than those with a rapid onset (such as oxazepam).¹² Women may demonstrate a more robust response than men to benzodiazepines, thereby requiring lower doses.¹³

Prospective and retrospective clinical trials that involve large numbers of pregnancies were unable to find an association between diazepam use and facial clefts or other defects in the infants.^{14,15} A report by Bergman et al¹⁶ investigated 80 pregnancies in which mothers who received Medicaid received ≥ 10 prescriptions for benzodiazepines during pregnancy. Of the 64 live births, 6 children had congenital anomalies. There was a high incidence of other substance exposures that included alcohol, however, which may have explained the detected abnormalities. In follow-up studies of children who were exposed prenatally to benzodiazepines, Laegreid et al^{17,18} reported reduced head circumferences and transient impairments of gross motor development that resolved by 18 months.

Infants who were born to habitual diazepam users may demonstrate withdrawal symptoms. Even limited use close to labor may cause the infant to appear “floppy” with hypotonia, decreased sucking, cyanosis, and impaired temperature regulation.¹⁹ Repeated small doses of oxazepam (30-45 mg daily) in 6 mothers did not result in any cases of a floppy infant.²⁰ This absence may be explained by the lack of active metabolites of oxazepam and by its relatively short half-life. Neurobehavioral effects have been observed in rats, but permanent behavioral alterations in humans that can be attributed to prolonged benzodiazepine exposure have not been proved.^{21,22}

Carbamazepine, an anticonvulsant with mood stabilizing properties, has been prescribed extensively in

Europe, and to a lesser extent in the United States, for alcohol withdrawal. In randomized trials of nonpregnant adults, carbamazepine was shown consistently to be at least as effective as benzodiazepines.²³⁻²⁵ It lacks the abuse potential of benzodiazepines and does not potentiate the depressant effects of alcohol.²⁶

Experience with carbamazepine use as an anticonvulsant during early pregnancy revealed an increased risk of spina bifida. The incidence of this anomaly is approximately 1% in exposed pregnancies, compared with a background risk of 0.1% to 0.2%.²⁷ Because folate supplements decrease the incidence of open neural tube defects, it customarily is recommended periconceptionally for patients who are receiving carbamazepine.²⁸ The effectiveness of folate supplements in preventing xenobiotic-associated spina bifida has not been established, however.^{29,30} Developmental delays have been observed in certain studies that investigated anticonvulsants. This conclusion, based on small numbers of exposed offspring, is questionable because of a lack of information on the socioeconomic status of the population, the absence of a control group, and a failure to allow for a normal distribution of test scores in the drug-exposed children.³¹ Additional studies are needed to clarify this possibility of developmental delay from prenatal exposure to carbamazepine.

Another anticonvulsant, valproic acid, has been used to treat alcohol withdrawal, although experience is more limited. Two double-blind studies in nonpregnant adults found valproic acid to be more effective than either carbamazepine or a placebo in the prevention of alcohol withdrawal symptoms and seizures.^{32,33} The well-known teratogenic effect of valproate precludes its use during pregnancy. Features of a human “fetal valproate syndrome” are similar to those of the fetal hydantoin

syndrome, which include growth restriction, facial dysmorphism, and limb and heart defects.³⁴ Of additional concern are data that indicate a 1% to 2% incidence of neural tube defects, specifically lumbar meningocele.³⁵ The mechanism of toxicity from valproic acid on neural tube closure is not folate-dependent, although folic acid supplements are usually prescribed.³⁶ Immediate and long-term cerebral dysfunction are potential concerns. According to Koch et al,³⁷ cord serum concentrations of valproic acid at birth correlated with the degree of neonatal hyperexcitability and neurologic dysfunction when children were re-examined 6 years later. More experience is required to support this observation.

Clonidine is an α -2 antagonist antihypertensive agent that is used in alcohol and opioid withdrawal. Clonidine is effective in reducing the autonomic arousal that characterizes alcohol withdrawal but not in preventing seizures or delirium. Because of its hypotensive effects and rebound hypertension, observation of vital signs must accompany the use of clonidine. Clinical studies that involved >200 pregnant women who received clonidine for hypertension during the second and third trimesters did not associate this agent with significant adverse fetal effects.³⁸ Transient hypertension in newborn infants appears to be uncommon.³⁸ The possible behavioral teratogenicity of clonidine was suggested by data that indicated that exposed children manifest hyperactivity and sleep disturbances, when compared with a control population.³⁹

Patients who abuse alcohol often have poor nutrition and suffer from B-vitamin deficiencies that can lead to neuropsychiatric problems (such as Wernicke's encephalopathy and Korsakoff's syndrome). It is customary to prescribe 100 mg of oral thiamine (vitamin B-1) daily during the detoxification period. Thiamine is transported actively across the placenta.⁴⁰ Although this dose exceeds the recommended dietary intake of 1.5 mg per day, we found no studies on the effects of excessive thiamine use during human pregnancy.⁴¹

Preventing or minimizing relapse

Disulfiram, approved by the FDA in 1952 for the abstinence phase of alcohol dependence, inhibits aldehyde dehydrogenase that leads to an accumulation of acetaldehyde when alcohol is ingested; symptoms of the disulfiram-alcohol reaction include facial flushing, tachycardia, hypotension, nausea, vomiting, and general malaise. Disulfiram treatment has met with mixed results in controlled studies of nonpregnant adults.⁴² Certain persons may not feel capable of abstinence without it and may wish to continue disulfiram for alcohol avoidance during gestation. Because evidence is so scant, it may be prudent to avoid disulfiram during pregnancy. It is postulated that developmental toxicity

from high levels of acetaldehyde is possible among pregnant women who drink alcohol and take disulfiram. Nonspecific fetal abnormalities have been reported with first trimester exposure, although this effect may be overestimated.⁴³⁻⁴⁶ Furthermore, available reports are insufficient to indicate whether congenital abnormalities in disulfiram-exposed fetuses resulted from the drug, alcohol-drug interactions, or other factors.

Naltrexone was the second medication to receive an FDA indication for alcohol dependence.⁴⁷ Alcohol stimulates the endogenous opioid system indirectly, thereby mediating reward (the "high"), which is necessary for addiction to occur. Naltrexone is an opioid antagonist that seems to dampen the positive reinforcement of alcohol.⁴⁸ Naltrexone does not impair implantation or viability of early mouse embryos or increase congenital malformations in rat or rabbit offspring.^{49,50} There is evidence, however, that animal offspring that are exposed prenatally to naltrexone have altered behavior. These effects include a facilitation of sexual behaviors in exposed male rats.⁵¹ Although published experience in humans is lacking, a preliminary study by Hulse et al⁴⁸ of 26 women with variable exposure to naltrexone did not detect any gross abnormalities in fetal development. Recent findings suggest that naltrexone may be less effective for women than for men with alcohol dependence. In a phase III trial of a depot injectable formulation of naltrexone, investigators found a statistically significant effect on heavy drinking in male subjects with both doses of naltrexone used in the study but no significant effect in female subjects.

Acamprosate (calcium homotaurinate) is a derivative of the natural amino acid taurine that seems to restore normal glutamate transmission, thereby reducing the hyperexcitable state from chronic alcohol use. Acamprosate has no abuse potential and no known drug interactions. A review of 16 European controlled trials that involved >4500 nonpregnant alcohol-dependent patients indicates that those patients who are treated with acamprosate are more likely to finish outpatient treatment and undergo a longer period of abstinence than patients who are given placebo.⁵²

Unlike disulfiram and naltrexone, acamprosate is not currently FDA-approved for this indication. We were also unable to locate any reports about acamprosate use in pregnant women.

Opioid dependence

Signs and symptoms of opioid withdrawal can be understood as a physiologic rebound from their chronic effects on brain function. Opioids or opiates act by binding to specific types of opioid receptors (μ , δ , and κ) that are distributed throughout the central nervous system. The phenomenon of cross-tolerance

Table III Currently available medications as antiaddictive therapy during pregnancy

Medication	Dosage	Important side effects	Clinical considerations
Opioid dependence			
Clonidine	0.1-0.2 mg/every 4-6 hours with monitoring of withdrawal symptoms	Hypotension and sedation	More effective for somatic than psychologic symptoms; will require adjunctive drugs
Naltrexone	50 mg/d or 100 mg Monday and Wednesday and 150 mg Friday	Abdominal pain, elevated liver enzymes in patients > 40 years old	Maintenance and withdrawal; do not administer if opioids have been used within 1 wk
Buprenorphine	2-4 mg for induction up to a maximum of 8 mg on first day; 2nd day dosages up to 16 mg/d, depending on symptoms; may be given every other day at 8 mg; dosage above 60 mg usually more effective	Mild withdrawal symptoms, constipation, sedation	Maintenance and withdrawal; only office-based treatment; do not use within 24 hours of opioid use.
Methadone	Dosage above 60 mg usually more effective	Sedation, constipation, decreased libido, ankle edema	Maintenance of opioid dependence; restricted to licensed narcotics treatment program
Smoking cessation			
Nicotine patch	4 wk of 21 mg/24 h then 2 wk of 14 mg/24 h, then 2 wk of 7 mg/24 h (Nicoderm CQ); 15 mg/16 h (Nicotrol) 8 wk as effective as longer periods	Local skin irritation, insomnia	Lower patch dose in those smoking <10 cigarettes/d; place new patch on different site daily; over-the-counter form; use only if risks of continued smoking outweigh risks of inhaler
Nicotine gum	Each piece of gum 2 mg for those who smoke <25 cigarettes and 4 mg for those who smoke >24 pieces/d	Jaw and mouth soreness, hiccups, dyspepsia	Schedule doses 1 piece every 1-2 hours rather than as needed; do not eat or drink 15 minutes before chewing or during chewing; over-the-counter form; use only if risks of continued smoking outweigh risks of inhaler
Bupropion sustained release	Begin 1 wk before quitting smoking; start with 150 mg each morning for 3 days, then 150 mg twice daily for 7-12 wk; may be used up to 6 mo	Insomnia and dry mouth; contraindicated with a history of seizures, eating disorders, head injury, or in those who have used an monoamine oxidase inhibitor in 14 days; pregnancy class B	Prescription; alternative for those who do not want nicotine replacement
Alcohol withdrawal			
Chlordiazepoxide	25-100 mg per dose	Sedation, dizziness, ataxia, confusion	Long half-life; may be loaded to symptom resolution, then discontinued
Oxazepam	15-60 mg per dose	Same as chlordiazepoxide	Shorter half-life; no active metabolites and not dependent on hepatic metabolism; generally requires dosing every 4-6 hours
Carbamazepine	400 mg loading dose, then 200 mg 3 times daily, tapering over 5 days	Sedation, dizziness, ataxia, confusion, nausea and vomiting, bone marrow suppression	Effective for moderate-to-severe withdrawal, not well studied for severe withdrawal

(Continued)

Table III (Continued)

Medication	Dosage	Important side effects	Clinical considerations
Alcohol dependence			
Disulfiram	250-500 mg every other day- every day	Hepatitis, neuritis, peripheral neuropathy, disulfiram- alcohol reaction (if alcohol is consumed)	Efficacy is enhanced by mon- itoring of compliance; may also have efficacy for cocaine dependence
Naltrexone	Same as for opioid dependence	Same as for opioid dependence	Screen carefully for covert opioid dependence to avoid precipitating withdrawal; contraindicated in those who are anticipating sur- gery or needing narcotics for pain management

Breastfeeding is not encouraged when any of these medications is used daily for prolonged periods.

explains the efficacy of substituting 1 opioid for another. Like alcohol pharmacotherapy, drug treatment for opioid dependence involves detoxification and maintenance/relapse prevention phases. However, in opioid dependence the same medications often are used for both phases. Long-term abstinence after detoxification is uncommon, so chronic maintenance treatment is undertaken frequently, even during pregnancy. Although detoxification from alcohol can be lethal, withdrawal from opioids is not life threatening to healthy adults. Rapid opioid withdrawal may precipitate preterm labor, however, and may be fatal in neonates.

Methadone is a long-acting μ receptor agonist that is used for detoxification and maintenance treatment. Nearly 3 decades of research, mostly among men, has demonstrated consistently the benefits of methadone for narcotic addiction. Advantages include reductions in illicit drug use, human immunodeficiency virus infection, and criminal behavior. Methadone is safe, provided that it is prescribed correctly. Like other drugs for withdrawal treatment, the dosage of methadone should be individualized on the basis of signs and symptoms of withdrawal, craving, continued opioid use, and side effects. Daily doses of at least 60 mg are more effective than lower doses.

Current practice in the United States holds that, despite pregnancy, women who are opioid dependent should be maintained on the lowest effective dose of methadone. Randomized controlled trials demonstrate an approximate 3-fold reduction in heroin use and a 3-fold increase in retention in treatment relative to non-pharmacologic treatment.⁵³ Extensive evidence exists that nonpregnant patients who stay on methadone long term do much better than either those who receive brief detoxification or a planned taper from maintenance or those who discontinue treatment.⁵⁴ If detoxification is attempted, it should best be done in the second trimester.⁵⁵ A review of studies of planned detoxification followed by maintenance therapy found that approxi-

mately one third of the patients will abstain at 6 to 12 months.⁵⁶ A study of outcomes after discharge from methadone maintenance revealed outcomes to be poor for patients who leave treatment. Only 8% of planned discharges from therapy did well at follow up, as defined by abstinence from opioids, lack of abuse of other drugs or alcohol, or no new arrests.⁵⁷ We did not locate reports that associated human birth defects with prenatal exposure to methadone. A reactive nonstress test result is less likely when the test is performed 1 to 2 hours after a patient receives a maintenance dose of methadone.⁵⁸⁻⁶⁰ Fetal effects from chronic exposure include a lower birth weight, smaller head circumference, jaundice, and thrombocytosis.⁶¹⁻⁶³ It is difficult, however, to distinguish between effects from methadone and from other substances that are taken concomitantly.

The best understood effect from methadone in the newborn infant is physical dependence with subsequent withdrawal. Symptoms may not emerge until 48 hours after birth, regardless of maternal dose.⁶⁰ The maternal methadone dosage does not correlate with neonatal withdrawal. An explanation could be a trend toward a higher incidence of illicit drug abuse before delivery among women who took a ≤ 80 mg daily dose of methadone.⁶⁴ A daily dose of 50 to 150 mg is usually adequate, although higher doses or twice daily doses may be required during the third trimester because of physiologic changes of pregnancy. Observations by Kaltenbach and Finnegan⁶⁵ indicated that methadone-exposed infants function within a normal range of cognition at 1- and 2-year evaluations. Confounding factors must be considered when any lower developmental levels are reported among methadone-exposed fetuses. The American Academy of Pediatrics revised their recommendation that only women on ≤ 20 mg daily of methadone could breast feed to include women on higher doses.⁶⁵

L-*A*-acetylmethadol (LAAM) was approved in 1993 for the treatment of opioid dependence. Being a μ

receptor agonist, LAAM is very similar to methadone, except for having a longer half-life that permits alternate day dosing. Because of concerns about possible arrhythmias (prolonged QT interval) and sudden death, LAAM will soon no longer be manufactured.⁶⁶ Because women who become pregnant are generally changed to methadone, we were unable to locate any reports about the fetal effects from LAAM.

The FDA approved buprenorphine in 2002 as a treatment for opioid dependence. Buprenorphine, a partial opioid μ receptor agonist and κ antagonist, can be used alone or in combination with other medications for detoxification and maintenance treatment. If an opioid-dependent person has little or no agonist in her system and is in withdrawal, buprenorphine ameliorates the withdrawal. If an individual has a high level of receptor occupancy (eg, a methadone-maintained patient who took 120 mg of methadone 4 hours before treatment), buprenorphine may precipitate withdrawal. Several reviews concluded that buprenorphine is effective for heroin dependence for up to 1 year. Buprenorphine has been shown to significantly increase treatment retention (relative risk, 1.21-1.52) and to decrease the use of heroin.⁵³ Licensed physicians who complete the requisite 8-hour training may prescribe buprenorphine in their offices, unlike methadone or LAAM, which require a specially licensed facility. In a gender comparison with men who receive buprenorphine, women demonstrated higher rates of abstinence from opioids, better retention rates in treatment programs, and lower rates of positive urine analyses.⁶⁷ Recent detoxification studies of nonpregnant inpatients and outpatients revealed higher retention and abstinence rates because of greater ease of early withdrawal with buprenorphine than with clonidine.⁶⁸

Buprenorphine has been administered successfully to opioid-dependant pregnant women as a maintenance replacement opioid.⁶⁹⁻⁷¹ Placental transfer of buprenorphine may be less than that of methadone, thereby reducing fetal exposure and development of dependence.⁷² Two recent reports that included 2 women who conceived while on buprenorphine and 15 women who took the drug during pregnancy found there to be no complications during labor and delivery and with newborn infant adjustment.⁷¹ A review by Johnson et al⁷³ that involved approximately 300 pregnancies disclosed a relatively low incidence of neonatal abstinence syndrome. We did not locate any studies in humans that evaluated long-term effects among exposed infants.

Naltrexone, a pure μ opioid antagonist, blocks all opioid agonist effects, including the euphoric effects that are mediated by the dopamine pathways of the mesolimbic system. Most studies of naltrexone in opioid-dependent patients have had strikingly high drop-out rates, presumably because of both its reward-blocking and its dysphoric effects in this population.⁷⁴

Buprenorphine therapy may be followed by naltrexone as maintenance therapy. An Australian study by Hulse et al⁷⁵ reported about the safe use of naltrexone for the detoxification of 18 pregnant women and for maintenance therapy of 8 pregnant women. No obstetric complications were observed, and the normal-appearing infants had appropriate head circumferences and reassuring Apgar scores. In addition, preliminary results disclosed promising results with a naltrexone implant during pregnancy.⁷⁶

Adjunctive use of clonidine for inpatient opioid detoxification can be a safe alternative in select pregnant patients.⁷⁷ Clonidine is currently the only nonopioid medication used widely to treat autonomic signs (tachycardia, elevated blood pressure, agitation) during a rapid taper of methadone or buprenorphine. The intensity of withdrawal symptoms with clonidine is similar to methadone alone or in combination with clonidine, but symptoms resolve more quickly with clonidine.⁷⁸ Sedation and hypotension are treatment-limiting side effects of clonidine.

Nicotine dependence

FDA-approved medications for smoking cessation include several nicotine replacement therapies (gum, transdermal patch, lozenge, inhaler, and nasal spray) and an antidepressant (bupropion). There is no quantity criterion (eg, number of cigarettes smoked daily) for prescribing an antiaddictive medication, although one-half pack per day is considered to be excessive. An extensive body of research on pharmacotherapy of nicotine dependence includes >6000 studies and 50 meta-analyses.⁷⁹ The use of replacement treatments approximately doubles the rate of cessation from approximately 10% to 20%.⁸⁰ When psychosocial treatment is also provided, a success rate of 15% to 30% per attempt at smoking cessation can be expected among persons who use 1 of the first-line treatments.⁸¹ Emerging evidence indicates that combining a passive form of therapy (eg, the patch) with an active form (eg, gum or inhaler) improves the odds of quitting, particularly in patients who failed monotherapy. The nicotine patch (21 mg, 14 mg, 7 mg), gum (4 mg), and lozenge (2 mg) are nonprescription, and preliminary studies indicate that they are as effective over the counter as when prescribed.⁸²

Concentrations of nicotine in the placenta, amniotic fluid, and fetal serum are consistently higher than in maternal serum.⁸³ Nicotine produces vasoconstriction and elevates blood pressure in a dose-dependent manner. Although an association between maternal smoking and fetal palate defects may be linked to a particular genetic susceptibility, most investigations implicate neither nicotine exposure nor cigarette smoking as increasing the risk of human congenital anomalies.⁸³

Epidemiologic studies consistently have found an association between maternal smoking and spontaneous abortion.⁸⁴⁻⁸⁶ Nicotine impairs fetal growth, possibly through a reduction in uterine blood flow.⁸⁷

According to Wright et al,⁸⁸ the maternal pharmacokinetics of a nicotine patch (21 mg for 6 hours) is unaffected by previous smoking, once smoking was ceased several hours beforehand. A similar study found nicotine kinetics in smokers to be similar when they used a nicotine patch or when they smoked.⁸⁹ Blood flow velocity in the uterine vessels and in the fetal middle cerebral artery were also similar for these 2 exposure conditions. Ogburn et al⁹⁰ reported that women in their third trimester who wore the nicotine patch for 4 days maintained serum nicotine and cotinine levels that were similar to those when they smoked. The only fetal alteration from nicotine exposure was a decrease in heart rate, but this effect was not judged to be clinically relevant.⁹⁰ Monitoring blood levels of nicotine may aid in the choice of the lowest effective dose and in the selection of the best route of nicotine delivery.

The antidepressant bupropion may aid in smoking cessation. According to an article in the Cochrane Database, the odds ratio for smoking cessation is 1.97 after bupropion use.⁹¹ This medication may be given to pregnant women who smoke one-half pack or more per day and who remain unresponsive to nicotine replacement therapy. Bupropion has not been associated with an increase in congenital defects in experimental animal studies. In September 1997, the manufacturer organized a registry that monitored 401 pregnancies prospectively, with 270 exposures being during the first trimester.⁹² By June 2003, 261 normal births occurred; 40 pregnancies ended in spontaneous pregnancy loss; 11 pregnancies involved induced abortions, and 9 pregnancies led to live births of infants with birth defects.⁹² Anomalies included 7 infants with heart abnormalities (valve and septal defects; coarctation of aorta), 1 infant with bilateral club feet, and 1 infant with Klinefelter's syndrome with no physical abnormalities. Although data in the registry are insufficient to determine whether bupropion increases the risk of heart or other congenital defects, monitoring will be intensified, which will include a focused retrospective cohort study.⁹²

Gender differences affect responses to treatment for nicotine dependence.⁹³ Women may manifest greater sensitivity to nicotine and thus undergo more severe withdrawal at a given level of nicotine consumption. Depression is more common in women, and nonpregnant women with depression respond more robustly to bupropion for smoking cessation.

Stimulant dependence

Currently, there is no FDA-approved or clearly effective medication for the treatment of cocaine,

amphetamine, or other stimulant dependence. Most pharmacotherapies for addiction to stimulants reduce the symptoms of a protracted withdrawal and craving, although there are investigational agents that also aim to reduce the rewarding effects of stimulants. Protracted withdrawal can last weeks to months and may lead to a relapse. A physiologic rebound of intoxicating effects explains many of the withdrawal symptoms: dysphoria, fatigue, irritability, difficulty concentrating, depression, somnolence, hyperphagia, and intense craving. Frequently in stimulant abuse research, promising early findings with certain medications are not been confirmed with larger, more rigorous investigations.⁹⁴

Recent studies by Kampman et al^{95,96} provide evidence that suggests that amantadine and propranolol may benefit patients with severe withdrawal symptoms. Women may metabolize amantadine more slowly than men. Although case reports indicate healthy infants being born after exposure to the drug, amantadine is not recommended during pregnancy without clinical trials.⁹⁷

Drug trials for cocaine addiction include dopamine agonists, lithium, amino acids, and vitamins. No experience with these medications has been reported during gestation, however; and none is clearly effective in nonpregnant substance users. Several studies suggest that women respond less robustly to tricyclic antidepressants than do men. Women obtain higher levels of imipramine, particularly when given with oral contraceptives, which extend the half-life of the antidepressant.⁹⁸ A recent well-conducted investigation by Simon et al⁹⁹ concluded that there was no association between prenatal tricyclic exposure and congenital malformations or developmental delay.

Cannabis dependence

Marijuana from cannabis plants is the most common illicit drug used during pregnancy. It is taken commonly in combination with alcohol, tobacco, and other illicit substances. Several active compounds with various effects are found in cannabis plants, but the primary active agent is delta-9-tetrahydrocannabinol. Placental transfer of delta-9-tetrahydrocannabinol has been well documented in animals and humans.^{100,101}

There is no indication that a pattern of minor malformations results from marijuana use.¹⁰² Although an association between its exposure during early pregnancy and fetal gastroschisis was raised in 1 case-control study of 110 infants (odds ratio, 3.0; 95% CI, 1.3-6.8),¹⁰³ a meta-analysis of reports that are available through 1996 did not find a significant association between maternal cannabis use and birth weight when effects from cigarette smoking were controlled.¹⁰⁴ Evidence of

postnatal problems in children who are exposed prenatally to marijuana is both limited and inconsistent.

Currently, there are no pharmacotherapies for cannabis dependence. Although addictive, cannabis generally produces only a mild abstinence syndrome; therefore, antiaddictive treatment of withdrawal is considered rarely. Advances in understanding the endogenous cannabinoid system may lead to new treatments for cannabis dependence and to new therapeutic applications of cannabinoid receptor agonists and antagonists.

Clinical applications for the obstetrician

Obstetricians have an ethical obligation to ask universal screening questions about substance use and to determine when to implement a brief intervention and selectively refer affected patients to receive counseling and medical care that is state-of-the-art, comprehensive, and effective. Progress in addiction pharmacotherapy will depend on success in 2 areas: (1) increasing the availability and usefulness of the agents that are currently prescribed and (2) focusing on new classes of drugs, passive immunizations, or drugs for co-occurring conditions. Because of the special maternal and fetal risks that are associated with pregnancy, we recommend a trial of psychosocial treatment before trying pharmacotherapy for alcohol or nicotine dependence in pregnant women. Risk/benefit ratios of those drug treatments are difficult to quantify. Opioid dependence and moderate-to-severe alcohol withdrawal should be treated medically with a lower threshold and more aggressively with pharmacotherapy, regardless of pregnancy, with concomitant counseling.

Decisions about who should prescribe antiaddictive medications for pregnant women depend on the substance use disorder and on what resources are available. Adjunctive drug therapy can be provided by a physician or any other health care provider with adequate training and experience, either in the office of an obstetrician-gynecologist or more commonly in an addiction treatment setting. For example, nicotine dependence alone is often treated in primary care settings, and the obstetrician is a highly appropriate person should the decision be made during pregnancy. Under most other circumstances, treatment is provided in a specialized, integrated treatment program for pregnant substance abusers. Treatment with methadone must occur under the auspices of a specially licensed program. Buprenorphine may be prescribed in an office setting, but if it is to be used in pregnant women, we recommend that it be prescribed by an addiction specialist who works in collaboration with women's health specialists. If medical detoxification from alcohol is necessary, it also should be overseen by an addiction specialist.

As antiaddiction pharmacotherapy advances, it is of critical importance that attention be focused on the effects of medications among special populations (such as reproductive-aged women, pregnant women, and their fetuses). Women should be included in pharmacologic trials when possible, and gender effects such be reported when the number of subjects is sufficient. Pregnant women are generally excluded from phase 3 trials, so it is essential to conduct phase 4 trials in pregnant women when it is ethical to dose. One important example is the need for controlled studies of buprenorphine in pregnant women.

Attention must also be placed on special patterns of psychiatric comorbidity in pregnant women with substance use disorders. High rates of affective disorders and of anxiety disorders, which includes posttraumatic stress disorders, are found among pregnant women. Finally, outcome studies of infants and children who are born to women who are receiving antiaddictive medications, which includes careful control for other substance use, are necessary to search for short- and long-term physical and behavioral impairments. By exploring solutions to these needs, the future should offer gradual and continual advances in addiction pharmacotherapy to benefit pregnant women and future generations.

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